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JOSEPH W. ENGLAND'S FAT-FREE TINCTURE OF DIGITALIS.¹

BY ELBRIDGE G. CUTLER, M.D., BOSTON.

In July, 1899, my attention was called to tincture of fat-free digitalis by Mr. Edward S. Kelley, of the firm of Kelley & Durkee, of Boston. This is a preparation devised by Joseph W. England, chief druggist of the Philadelphia Hospital, Philadelphia, to meet the serious drawback of bulk in the use of the infusion of digitalis when large doses are required to secure the desired needs of action on the heart and kidneys.

Mr. England, in 1892,² presented a paper to the Pennsylvania Pharmaceutical Association on the subject of infusion of digitalis. In discussing the subject of digitalis leaf, he said that the term digitalin had been given to a variety of products, but was generally reserved for the compound obtained by Schmiedeberg in 1875. He found that the commercial digitalins, whether crystalline or amorphous, were varying mixtures of Schmiedeberg's digitalin, digitoxin, digitonin, digitalein, and certain decomposition products. Of these, all except digitoxin were believed to be glucosides. Neglecting the decomposition products, these principles could be grouped best into two classes according to solubility: (1) Those soluble in alcohol and insoluble or almost insoluble in water; (2) those soluble in both water and alcohol. Digitalin and digitoxin would be assigned to the first class, and digitonin and digitalein to the second class, the tincture and fluid extract containing most largely digitalin and digitoxin, with some digitonin and digitalein, while the infusion contained digitonin and digitalein with no digitalin or digitoxin. Hence the difference in clinical value between the aqueous and alcoholic preparations of digitalis leaves. Mr. England spoke of the superior therapeutic worth of English over German leaves and this was ascribed to the fact of the English leaves being carefully freed from nerves and stalks (which had been shown to contain only one-fifth as much digitalin as the leaf parenchyma), thereby reducing the element of variation to a minimum. Since 1892, however, Mr. England (through personal advices from London) found that much of the so-called English leaves are simply very carefully sifted German leaves, and not English cultivated leaves, as was supposed. He also called attention to the fact that the freshly made infusion was feebly acid in reaction, while the tincture gave the acid action more promptly, owing, as he thought, to a greater solubility of the acids of the leaf in alcohol and the presence of a larger quantity in solution. The acids present in digitalis leaves are the odorous antirrhinc acid of Morin (1845) and the fatty digitoleic acid of Kosmann. The percentage of fixed oil obtained by petroleum benzine extraction and spontaneous evaporation was relatively high. In 1887 he obtained about 5%. The oil contained a volatile portion and a fixed oil. It was a dark reddish-brown liquid of heavy, persistently narcotic odor, largely soluble in alcohol, freely soluble in ether or chloroform and not readily inflammable, showing the absence of any trace of petroleum benzine. It left a permanently greasy stain on bibulous paper. Its specific gravity was about .850. Heated for eight hours it lost 5.4%, and also

¹ Read before the Clinical Section of the Suffolk District Medical Society, March 21, 1900.

² American Journal of Pharmacy, July, 1899, pp. 332-344.

lost its peculiar narcotic odor, becoming more fatty, thus indicating the loss of a volatile portion.

Tincture of digitalis, when given any way, sometimes causes profound gastric disturbance, even nausea and vomiting. Mr. England, believing that possibly this might be due in part, if not wholly, to the fixed oil in the leaf and its free acid, prepared some years ago a so-called fat-free tincture in which these two principles were eliminated.

For the past five years the tincture of fat-free digitalis made by Mr. Joseph W. England, to replace the official tincture, has been used in the wards of the Philadelphia Hospital. Dr. Daniel E. Hughes, chief resident physician of the Philadelphia Hospital, makes the following clinical statement to Mr. England, and it is printed in this paper:

"The vast majority of the cardiac and nephritic patients coming to the Philadelphia Hospital have had as a marked and subordinate complication chronic gastric catarrh, and could not stand the administration of the official digitalis tincture, but could take our more bulky infusion. To secure the desired cardiac and nephritic action of this valuable drug required large doses of the infusion, which was a very serious drawback to its use. Mr. England's attention was called to the subject, and he suggested that he might be able to prepare a tincture of digitalis of the same strength as the official preparation, but devoid of the nauseating proximate principles of the latter. He prepared his preparation, and we submitted it to extended employment. After the continued use of this particular preparation of digitalis I can speak of its efficiency and non-nauseating properties. I am confident that it is much more promptly absorbed than the official tincture and this makes the cumulative action of this drug almost, if not altogether, *nil*. Again, more prompt absorption is shown by its quicker action upon the heart, and increase in the flow of the urine.

"The non-irritating properties of this special tincture of digitalis are forcibly shown by its hypodermic use, abscesses having never followed its use, while the official tincture almost invariably causes pain, swelling and abscess formation from hypodermic use."

Mr. England makes his fat-free tincture of digitalis by exhausting the leaves while freshly ground to a No. 60 powder with purified petroleum benzine, either by maceration with solvent in excess for forty-eight hours, if in small quantities, or by maceration and subsequent percolation, if in large quantity, repeating the solvent treatment until all the fat, etc., is removed. The residue is then dried by exposure to air, taking care that no particle of benzine odor remains. While benzine is very volatile, the last portions of it volatilize rather slowly relatively when spontaneously evaporated, especially if adherent to vegetable structure. Exposure of the residue to sunlight, as well as to open air, he says yields the best results.

After the benzine treatment, the dried and powdered leaves are made into a tincture according to the process for the official product, 150 grammes of leaves being used to make 1,000 cubic centimetres with dilute alcohol, with this difference that the reservoir is removed when the total percolation amounts to 980 cubic centimetres, and it is then carefully neutralized with a sufficient quantity (about 10 or 15 cubic centimetres) of the official 10% ammonia water, and the

product is made to measure 1,000 cubic centimetres with fresh percolate or diluted alcohol, or, as he gives it, with the usual weights and measures 1,094 grains of the powdered leaves may be exhausted with dilute alcohol to yield 15½ fluid ounces, and then about 1 or 2 fluid drachms of 10% ammonia water will be required to effect neutralization, after which sufficient percolate or diluted alcohol should be added to make the whole product measure 1 pint. After standing for twenty-four hours the newly made tincture usually precipitates some coloring matter, etc., which should be removed by filtration through paper.

The product as finally obtained is a deep, reddish-brown, almost black, liquid, keeping perfectly for years, of not unpleasant odor and a pure bitter taste. It does not have the acid odor or taste of the official tincture and, unlike the latter, does not become turbid on admixture with water, but remains transparent with any amount of dilution.

The purposes of this procedure are two-fold: (1) The benzine treatment removes the fat and probably all the nauseating odorous principles; (2) the ammonia treatment neutralizes the free acids present in the leaf, forming the ammonium salts.

It does more than this. The neutralization with ammonia makes all the proximate principles in the tincture water-soluble and not partly so as in the official product. (When the official product is diluted with water, it precipitates.) This is especially valuable for the reason that all compounds before absorption by tissues must first be made soluble before they can be absorbed. By this means absorption is facilitated and assimilation is hastened, as will be shown by pharmacological results later.

"When the fat-free tincture was first made, the object was to obtain a preparation which would not nauseate, and clinical results in the Philadelphia Hospital have shown that this end is very generally accomplished. A short time ago, however, an even more valuable feature of the fat-free tincture became evident. This was the *rapidity* with which the preparation was absorbed and assimilated in comparison with the official product. Observations were then made to determine clinically the relative rapidity with which the fat-free tincture and the official tincture were each absorbed, noting, (1) the time of primary effect; (2) the time of maximum effect; and (3) the pulse reduction or work, both in male and female patients and both hypodermically and by the mouth."

This work was performed by Mr. England with the assistance of Dr. F. A. Sherrer. Great care was exercised in obtaining patients in whom the physical conditions were as nearly uniform as possible, so that comparative results could be had. The cases chosen were mostly rheumatic with endocarditis. Patients were given the tinctures three hours after meals, when the stomach was practically empty, the fat-free tincture one day, the official the next. No food or water was taken during the time of administration. The beginning of each administration was so timed that there was no serious difference between the rate of pulse beats when the giving of each preparation was commenced. At most the primary time was never more than 6 beats. It is obvious that if a heart is beating almost normally one day when one tincture is given, and is beating tumultuously the next day when another tincture is used, that uniform conditions do not exist, and comparative results can-

not be had. The next essential is rest in bed and perfect quiet. No sphygmographic tracings were made to determine the rapidity of absorption and action more accurately, but the preliminary trials made by the mouth showed that primary effects were obtained with fat-free tincture in about fifteen minutes, and primary effects with the official tincture in about thirty minutes. The tinctures were both made from Allen's digitalis leaves. The fat-free tincture was made in January, 1898, the official in September, 1898. The following are some of the results which were obtained:

CASE I. Male patient; tinctures given by mouth; doses, 10 minims.

Fat-free tincture. March 29, 1899.		Official tincture. March 30, 1899.	
Pulse.	Time.	Pulse.	
90	3.45 P. M.	86	
88	4.00 "	86	
88	4.15 "	82	
86	4.30 "	82	
84	4.45 "	80	
82	5.00 "	80	

Fat-free tincture.—Primary effect in fifteen minutes, full effect in seventy-five minutes; pulse reduction or work, 8 beats.

Official tincture.—Primary effect in thirty minutes, full effect in sixty minutes; pulse reduction or work, 6 beats.

CASE II. Male patient; tinctures given by mouth; doses, 10 minims.

Fat-free tincture. April 1, 1899.		Official tincture. April 2, 1899.	
Pulse.	Time.	Pulse.	
78	3.45 P. M.	80	
74	4.00 "	80	
73	4.15 "	78	
72	4.30 "	76	
71	4.45 "	73	
71	5.00 "	72	

Fat-free tincture.—Primary effect in fifteen minutes, full effect in sixty minutes; pulse reduction or work, 7 beats.

Official tincture.—Primary effect in thirty minutes, full effect in seventy-five minutes; pulse reduction or work, 8 beats.

CASE VI. Male patient; tinctures given hypodermically; doses, 10 minims. Same patient as Case II.

Fat-free tincture. April 17, 1899.		Official tincture. April 18, 1899.	
Pulse.	Time.	Pulse.	
58	9.30 A. M.	54	
54	9.45 "	54	
47	10.00 "	50	
46	10.15 "	50	
46	10.30 "	49	
48	10.45 "	51	
48	11.00 "	52	

Fat-free tincture.—Primary effect in fifteen minutes, full effect in forty-five minutes; pulse reduction, or work, 12 beats.

Official tincture.—Primary effect in thirty minutes, full effect in sixty minutes; pulse reduction, or work, 5 beats.

CASE IX. Male patient; tinctures given by mouth; doses, 10 minims.

Fat-free tincture. May 20, 1899.		Official tincture. May 31, 1899.	
Pulse.	Time.	Pulse.	
54	10.00 A. M.	54	
48	10.15 "	52	
48	10.30 "	48	
46	10.45 "	48	
46	11.00 "	44	asleep.
50	11.15 "	44	
52	11.30 "	46	

Fat-free tincture.—Primary effect in fifteen minutes, full effect in forty-five minutes; pulse reduction, 8 beats.

Official tincture.—Primary effect in fifteen minutes, full effect in sixty minutes; pulse reduction, 10 beats.

This is the only case in which primary effect took place in fifteen minutes with the official tincture; as the patient was in an especially quiescent state preparatory to sleeping, the tincture had less work to do than usual, and did it more quickly. The marked reduction of pulse beats is due to the same cause.

In all there were 15 cases examined. The following is a summary of results:

SUMMARY OF RESULTS.

Case.	FAT-FREE TINCTURE.			OFFICIAL TINCTURE.		
	First effect, minutes.	Full effect, minutes.	Work, or beats reduced.	First effect, minutes.	Full effect, minutes.	Work, or beats reduced.
1	15	75	8	30	60	6
2	15	60	7	30	75	8
3	15	60	5	30	90	5
4	15	45	8	30	75	6
5	15	45	6	30	60	5
6 h.	15	45	12	30	60	5
7 h.	15	45	10	30	60	6
8 h.	15	45	8	30	60	8
9	15	45	8	15 l.	60	10
10	15	30	6	30	30	2
11	15	—	9	30	105	9
12	15	45	6	30	60	8
13	15	45	10	30	45	6
14	15	45	3	45	105	6
15	15	60	8	45	45	4
Averages.	15	49	76	31	66	64

h. hypodermic cases; others, by mouth.
l. exceptional case, explained in text.

Twelve of the above patients were male, 3 female. In 12 of the cases the tinctures were given by mouth, 3 hypodermically. Mr. England arrives at the following conclusions: Of these results it may be said that practically the primary effects of the fat-free tincture were manifested in fifteen minutes, and the maximum in forty-five minutes; while with the official tincture primary effects were obtained in thirty minutes and the maximum in sixty minutes. In both cases, however, the duration of effect was the same, thirty minutes. The pulse reduction, or work, was slightly greater with the fat-free than with the official. The most striking difference, however, exhibited between the fat-free tincture and the official tincture was the *much greater rapidity of absorption* and action of the former, showing a speedy assimilation. The time element of direct action is a very important matter in some cases and might readily mean the difference between the life and death of a patient. No especial difference in the time of absorption between hypodermic injections and mouth administrations was observable, but when the tincture was given hypodermically the pulse reduction seems to have been greater with the fat-free tincture, though not extending over any greater length of time.

The short abstract of Mr. England's paper shown me by Mr. Kelley in one of the pharmaceutical journals was so convincing, coming as it did from such an authority, that I was eager to try the preparation, and

Mr. Kelley very kindly placed some of it at my disposal in a few days. This was early in August or late in July, 1899. The first patient to try it was a man of seventy odd, who had been a sufferer from cardiac disease for several years. Of late he had had broken compensation, shown by ascites and great edema of the legs, shortness of breath on exertion, frequent attacks of dyspnea, both by day and night, the latter especially severe, considerable cough, abundant expectoration, passive congestion of liver and spleen as shown by their great enlargement on palpation and percussion, passive congestion of the kidneys and digestive tract. He had no appetite, suffered from gastric oppression and distention after food, and felt generally miserable. He could only take the official tincture of digitalis in small doses for two days at a time with a week's respite, as it had been used for several years, and had frequently been pushed to its full limit of tolerance. Trial of the infusion was equally ineffectual because of the large dose and nauseating character of the preparation. From the very first dose the fat-free tincture agreed with the patient and he has been taking it uninterruptedly to the present time.

In another case where the official tincture of digitalis could not be used at all except for two days at a time, and where the drug was grievously needed, I have been enabled to give the fat-free form three times a day from the time I first began it in August till the present time, with the very best results. This patient was unable to endure even the smell of the ordinary preparation, although to my senses there was little difference in their odors. I have not used the preparation in the Massachusetts General Hospital sufficiently long (only since March 1st) to obtain any new ideas in regard to its action, but my experience of the past seven months has been confirmed with reference to its usefulness. This tincture does not do more than the official tincture will do, but it will not produce nausea or disturbance of the digestion as the latter may and frequently does do. In my experience it fills a place which is a very important one in practice, and I bring forward Mr. England's paper with the hope that the profession will be induced to make a trial of the preparation so as to see if the experience which has been recorded is correct, as seems to be the case now.

KNEE-JOINT SURGERY FOR NON-TUBERCULAR CONDITIONS.¹

A REPORT OF THIRTY-EIGHT OPERATIONS FOR SYNOVIAL FRINGES, INJURED SEMILUNAR CARTILAGE, LOOSE CARTILAGE, COAGULA, EXPLORATORY INCISION, ETC.

BY JOEL E. GOLDTHWAIT, M.D., BOSTON.

In presenting this subject it is my hope that from a study of the cases and in the general discussion something may be added to our knowledge of joint surgery. The cases which are presented are those in which the knee joint has been freely opened, either for diagnosis or to render the function of the joint more perfect. The cases in which operations have been performed which would tend to lessen the

normal use of the joint, such as excision or erosion, are excluded, as are also all cases in which the operation has been performed as a part of the treatment of the septic or suppurative processes. All of the cases included in this series were at the time of the operation sterile, so far as the condition of the joint was concerned. In all the knee was the joint operated upon, but while this joint must, from its size and anatomical structure, more often require such treatment than the others, nevertheless the same principles apply to any of the other articulations.

The age of the patients varied from four to sixty-five years, and this fact seemed to be of about the same importance as in other operations.

There is, as you all know, a popular impression that for some reason it is more dangerous to open the large joints than any of the other large cavities, and while this impression is less commonly held than formerly, yet even now because of it operations are refused and patients are condemned to long courses of non-operative treatment, which frequently is not only inconvenient, but may disturb to an irremediable degree the normal character of the joint structures. The reason of this fear is undoubtedly very largely due to the serious results which attended such operations in the pre-antiseptic days, and the statements which are to be found in the textbooks of those days have to a considerable degree influenced the writings of the more recent times. That opening a joint is more feared by the average surgeon than opening the cranium or the abdomen is partly due to these traditions, and is similar to the fear formerly felt in regard to these very operations which are now performed so commonly and so successfully. Similar changes will undoubtedly take place in joint surgery as it becomes more common and better understood, and the occasional unfortunate result will be easily overlooked in the great general good which will result from such work.

It is my personal feeling that there is no more danger in opening the knee or any of the other large joints than in opening the peritoneum. Neither operation should be performed carelessly or without due preparation, but in case the symptoms cannot be relieved in any other way, there should be no hesitation in resorting to the operation. To go still further, if there is any question as to the diagnosis, and the doubt means otherwise a long period of inactivity, with the danger of destructive changes taking place which could be prevented, there should be no hesitation in opening the joint to determine the exact nature of the disease, so that proper treatment can be prescribed. It is practically impossible at times to differentiate between some of the beginning rheumatoid diseases and tuberculosis in the same stage, and yet it is at this very time that it is of the utmost importance to know the exact nature, as the treatment of the two conditions is so radically unlike, and if sufficient time is allowed to elapse for the diagnosis to become clear, the disease is so far advanced that nothing more than imperfect results can be obtained.

In children this question of doubt does not so often arise, as at this time of life the majority of subacute or chronic joint affections are tubercular, and as in these tubercular cases early operative interference is so rarely indicated, the exploratory incision is less often necessary. In adults, however, where the non-

¹ Read at a meeting of the Surgical Section of the Suffolk District Medical Society, and at the meeting of the American Orthopedic Association, held in Washington, May 1, 2 and 3, 1900.