DIGITOXIN—A CRITICAL REVIEW*

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Within recent years, there has been an increasing interest in purified digitalis preparations. However, in spite of the original optimistic reports, the recent literature tends to discredit the value of the new preparations. Most criticisms fall into two groups: (A) Inadequacy of digitalization with the original recommended dosage schedules. (B) Increase in the incidence of drug toxicity. It is the purpose of this paper to analyze the value of the most commonly used purified glycoside, digitoxin.

History

Modern concepts of digitalis therapy began in 1785, with the publication by William Withering of his classical monograph,[86] *An Account of Foxglove and Some of Its Medical Uses, with Practical Remarks on Dropsy and Other Diseases.* Withering, a botanist as well as a physician, recognized that the amount of active material present in the plant was not constant, and he emphasized the importance of controlling the conditions of growth of the plant and the importance of proper selection of the leaves. He cautioned against using the roots because he had observed a great variation in the potency of material obtained from that source. During most of the 19th century Withering's advice was little heeded; purple foxglove was often prescribed indiscriminately and in toxic doses. But the striking clinical results sometimes obtained with such crude preparations stimulated chemists to begin the search for active principles.

The first studies recorded are those of the French chemist, Destouches, in 1808, and Quévenue and Homolle, in 1842, who probably already had digitoxin present in their digitaline preparations. In 1868, Nativelle[62, 63] isolated from the dried leaves of *Digitalis purpurea* a relatively pure cardio-active principle, which was given the name of digitaline cristallisée, and was proved to be a potent cardiac drug by Vulpian. It has been marketed in France by the name of digitaline Nativelle. In 1875, the German chemist Schmiedeberg reported[70] the isolation of a closely allied material, which he named digitoxin, and stated that it formed the bulk of digitaline cristallisée. Windaus,[85] in 1926, completed the analytical investigation of digitoxin by determining its empirical formula and by interpreting its behavior on hydrolysis.

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Opinions vary about whether or not these two substances are the same. While Weese[82] refers to them as identical, Jacobs[48] believes that the two products are not exactly the same and states that digitoxin is the chief constituent, probably at least 90 per cent of the original digitaline cristallisée of Nativelle. *New and Non-official Remedies* uses the names digitaline cristallisée (Nativelle) and digitoxin interchangeably. The *United States Pharmacopœia* also treats them as if they were the same. However, there is some belief[16, 24, 30, 41, 61] that preparations of digitaline cristallisée (Nativelle) and digitoxin differ in potency.

Pharmacology

At the present time, there is no synthetic cardiac glycoside for clinical use; all now sold are derived from the crude drugs. The chemical isolation of these pure principles is not a simple process; the final yield of glycoside is between ninety and one hundred per cent chemically pure.[23, 48, 76]

The empiric formula of digitaline Nativelle closely approximates $C_{41}H_{64}O_{13}$. It appears as thin colorless, odorless, elongated, rectangular platelike crystals with a bitter taste and a melting point between 253° to 263°C. It is practically insoluble in water, ether, and glycerin, and is soluble in acetone, chloroform, ethyl alcohol, and pyridine. It is standardized by the intravenous method of Hatcher and Brody,[46] so that 0.42 mg. equal one cat unit, but the therapeutic dose is much less than that of digitalis measured in cat units. The action of digitoxin is like that of digitalis, but is more persistent. The preparations available are in the form of tablets containing 0.05, 0.01, and 0.2 mg. of the active principle and in 2 cc. and 1 cc. ampoules containing 0.4 and 0.2 mg. respectively. Digitoxin has been shown to be completely absorbed from the gastrointestinal tract in animals and human beings.[13, 15, 19, 36, 45, 64] For that reason, the oral and intravenous doses are the same.[80] If the decline in the ventricular rate is used to judge the oral absorption of digitoxin, it is complete in from 4 to 10 hours.[40, 80] On intravenous injection, the initial effects were noted in from 25 minutes to 2 hours, with maximum effects in 2 to 9 hours. The effect begins to regress in 2 or 3 days, the total duration of action lasting approximately 2 weeks.[20, 22, 30, 35, 41] When given subcutaneously or intramuscularly, there may be considerable pain and local reaction. Sterile abscesses may result. Digitoxin is readily absorbed from the large bowel, and rectal administration is also a valid means of administering the drug. The fate of digitoxin, as with

digitalis, within the body is unknown. Ninety per cent of the drug is taken up by the extracardial tissues, especially the liver and skeletal muscles. Gram for gram, the heart muscle absorbs more than does any other organ in the body. Because of the persistence of the cardiac action of digitoxin after its administration is discontinued, it is essential to obtain a history of previous digitalis before further administration of the drug. Small amounts of the drug are excreted, unchanged, in the bile and urine.

The potency of 1 mg. of digitoxin is approximately equal to 1000 mg. (gr. 1.5) of U.S.P. XII digitalis powder and to 1 U.S.P. XII Digitalis Unit. A dose of 1.25 mg. of digitoxin induces the same degree of reduction of ventricular rate as 1.25 gm., or 16.3 cat units of whole-leaf digitalis. There is a slower rate of dissipation, and hence toxicity is more prolonged.[4] No significant difference has been found in the ratio between the toxic and therapeutic doses for digitoxin as compared to digitalis.[38, 39, 42, 54, 59]

Digitoxin, in patients with congestive failure, results in an increased cardiac output, a decrease in arteriovenous oxygen difference,[6, 31, 44, 50, 52, 53, 56, 57, 66, 71, 72, 74] lowered venous pressure,[12, 21, 32, 35, 52, 57, 72, 74, 75, 87] a faster circulation time,[32, 52, 74, 75, 87] and a diminished blood volume.[11, 58] After digitalization, the vital capacity is increased,[72, 74] the respiratory minute volume is reduced,[9, 44, 74] and the alveolar carbon dioxide is increased.[71] The basal metabolic rate falls,[71, 75] and there is decreased oxygen debt after exercise.[65] There is a slowing of the pulse rate in patients with auricular fibrillation and in those cases of congestive failure with a sinus tachycardia. This is brought about both by a vagal stimulation, which may be obliterated by atropine, and by a direct action on the nodal tissues and myocardium, which cannot be obliterated by atropine. Controversy still exists as to the exact mechanism of the action of digitalis. The theory of hepatic vein constriction probably does not apply in man.[2, 69] The action of digitoxin is primarily on the myocardium,[1, 22, 25, 26, 27, 35] as the effect on the vagus and on the conducting tissue does not account entirely for the beneficial response which may occur before or without a change in rate. Boyer and Poindexter[10] stated that the beneficial effect may be brought about in part by a cortin-like action on the myocardium, whereby potassium is maintained within the cell, and cell hydration is improved.

Therapeutically, the most important use of digitoxin is in congestive heart failure. It is useful regardless of whether the failure is predominantly of the right or left ventricle or both. The etiology of the heart

failure modifies the response to the drug. The best results are obtained when failure is due to hypertensive or arteriosclerotic heart disease. Decompensation due to severe rheumatic myocarditis, cardiovascular syphilis, toxic myocarditis, myxedema, hyperthyroidism, and thiamine deficiency is less responsive, if at all. Digitoxin is also indicated in auricular fibrillation and auricular flutter if failure is present. It is not contra-indicated in heart block when failure is present.[7, 79] Sometimes it is successful in the treatment of paroxysmal tachycardia.[14, 67] In coronary thrombosis with failure, it is indicated, but must be carefully regulated, and rapid digitalization is unwise. There is increased sensitivity of the injured myocardium to the drug.[3, 29, 81, 83] Travell et al.[81] reported that in a cat, ligation of a single coronary artery caused a reduction of 25 per cent in the fatal dose of digitalis. If coronary flow is diminished, less than an average therapeutic dose of the glycoside may cause toxic symptoms. In heart failure due to shock, cardiac compression from pericardial effusion or constricting adhesions, or in peripheral circulatory collapse as a result of acute infectious disease, the drug is of no value. It does not increase coronary blood flow and is not indicated in angina pectoris without failure.[8, 33, 34]

Toxicity

Digitoxin, when given in recommended dosage and despite care, frequently produces signs and symptoms of overdosage. The toxic actions of digitoxin were first observed by Koppe,[51] who took 3.5 mg. in 5 days, suffered severe toxic symptoms, with nausea and vomiting, slowing of the pulse rate from 80 to 40, and a bigeminal rhythm that became grossly irregular. Serious toxic manifestations seem to be more frequently observed with the use of the digitalis glycosides than from the whole-leaf preparations,[28, 47, 68, 84] and the incidence of toxicity has risen in direct relation to the increased use of these glycosides.[47]

The toxic symptoms and signs with variable dosage are different in different individuals. The resultant symptoms are due to continued ingestion of the drug in amounts greater than can be destroyed or eliminated from the body. There is an accumulation of the drug in the body, and among the earliest symptoms noted with digitoxin overdosage is anorexia, which usually appears before the nausea and vomiting. Diarrhea and abdominal pains occasionally occur. With digitoxin poisoning almost every clinically known type of cardiac arrhythmia can occur, i.e., sinus arrhythmia, premature contractions, bigeminy, trigeminy,

auricular fibrillation, auriculoventricular block, sinus bradycardia, paroxysmal auricular tachycardia and ventricularfibrillation. Digitoxin effect on the electrocardiogram is demonstrated by T wave changes, RS-T interval depression, P-R interval prolongation, and Q-T time shortening.

Rarely one sees the cerebral symptoms of overdosage such as convulsions, aphasia, and delirium, rather more commonly headache, fatigue, malaise, confusion, drowsiness, and disorientation. Visual disturbances are uncommon, but there may be blurring or disturbances of color vision in which objects appear yellow and green, less frequently blue and red. Amblyopia, scotomata, and diplopia may occur. Sensitivity to digitalis leaf is rarely reported and may be urticarial or scarlatiniform in character, accompanied by an eosinophilia. It has not been reported with digitoxin.

Therefore, whenever digitoxin is used, the appearance of signs of cardiac disorder must be watched for carefully, not only clinically, but with the aid of the electrocardiogram, and such appearance should call for the immediate discontinuance of the drug. Toxic symptoms may persist for a week or more.[18, 55, 77, 84]

Clinical use

Most patients receiving digitalis continue to require the drug for the remainder of their lives. After digitalization has been attained, the drug must be given daily in order to maintain the beneficial effect. A sufficient amount must be given to replace that which is eliminated and destroyed by the body. Wide variations exist from patient to patient regarding the maintenance dose, and that dose seems to bear no relation to body weight, or to type or severity of heart failure. The rate of excretion varies from day to day and from person to person, depending upon the amount of the drug within the body. It has been shown that the patient does not excrete a fixed amount each day, regardless of the dose given, but, rather, a certain fraction of the amount present in the body. An equilibrium becomes established between the amount of the drug within the body and the rate of elimination. The excretion rate is limited, however, and, with excessive doses, the drug accumulates in the body to a point where toxic symptoms occur. One seeks to give an amount which will restore the highest degree of cardiac efficiency and relieve all symptoms and signs of heart failure, and sometimes this dose borders on the toxic.[5, 17, 37, 49]

No.	Age and sex	Etiologic	Anatomic	Degree of failure	Wt. (lbs.)	Initial Digitalization*	Toxic effects
10	70 F	Arteriosclerotic heart disease	Enlarged heart coronary sclerosis myocardial fibrosis	++++	85	0.4 mg. daily for 3 days	After 4 days severe nausea, vomiting, 1 Heart block, ST depression in all leads, AV conduction .22, drug stopped for one week; dose then reduced to 0.1 mg. daily, no toxic symptoms since.
11	45 F	Arteriosclerotic heart disease	Coronary sclerosis myocardial fibrosis	++	114	0.6 mg. with repeat in 6 hrs.	After 20 days marked nausea and vomiting; drug reduced to 0.1 mg. daily, no toxic symptoms since.
12	41 M	Hypertensive heart disease	Enlarged heart	++	190	0.2 mg. daily	After 7 months marked nausea and vomiting; changed to whole-leaf digitalis.
13	74 F	Arteriosclerotic heart disease	Coronary sclerosis myocardial fibrosis	++	155	0.2 mg. daily	After 3 months yellow vision; drug reduced to 0.1 mg. daily; no toxic symptoms since.
14	61 F	Hypertensive arteriosclerotic heart disease	Enlarged heart coronary sclerosis myocardial fibrosis	+	135	0.2 mg. daily	After 3 months marked nausea and vomiting, and yellow vision; drug reduced to 0.1 mg. daily and no toxic symptoms since.
15	64 F	Hypertensive arteriosclerotic heart disease	Enlarged heart coronary sclerosis myocardial fibrosis	++++	172	0.4 mg. every 4 hrs. for 3 doses	After 26 days nausea, vomiting, anorexia, drowsiness and weakness, drug reduced to 0.1 mg. daily and no toxic symptoms since.
16	58 M	Arteriosclerotic heart disease	Coronary sclerosis myocardial fibrosis	++	150	0.4 mg. one dose	After 4 days diarrhea and yellow vision; dose reduced to 0.1 mg. daily, no toxic symptoms since.
17	57 M	Hypertensive heart disease	Coronary sclerosis	++	190	0.8 mg. with 0.4 mg. after 6 hrs.	After 4 months, anorexia, nausea, and vomiting. Dose reduced to 0.1 mg.; no toxic symptoms since.
18	67 M	Hypertensive heart disease	Enlarged heart	++	154	1.2 mg. single dose	After 1 week nausea and vomiting. Dose reduced to 0.1 mg.; no toxic symptoms since.
19	65 M	Arteriosclerotic heart disease	Coronary sclerosis myocardial fibrosis	++	190	0.6 mg. with repeat dose after 6 hrs.	After 3 months dizziness and nausea. Dose reduced to 0.1 mg. daily; no toxic symptoms since.
20	68 M	Arteriosclerotic heart disease	Coronary sclerosis myocardial fibrosis	+	150	1.2 mg. single dose	After 1 year pulse down to 46, nausea and vomiting. Dose reduced to 0.1 mg. daily; no toxic symptoms since.

*Maintenance dose 0.2 mg. daily.

No.	Age and Sex	Etiologic	Anatomic	Degree of failure	Wt. (lbs.)	Initial Digitalization*	Toxic effects
1	40 M	Arteriosclerotic heart disease	Coronary sclerosis myocardial fibrosis	+++	160	0.6 mg. with repeat in 6 hrs.	Marked nausea and vomiting; dose reduced to 0.1 mg. daily, but symptoms continued; changed to whole-leaf; symptoms stopped.
2	61 M	Arteriosclerotic heart disease	Coronary sclerosis myocardial fibrosis	+	145	0.2 mg. daily	After 21 days marked nausea and vomiting, dose reduced to 0.1 mg. daily and symptoms ceased.
3	75 F	Hypertensive arteriosclerotic heart disease	Enlarged heart coronary sclerosis	++	160	0.2 mg. twice daily for 6 days	Took 1.0 mg. and marked nausea and vomiting appeared. Reduced to 0.1 mg. daily; no symptoms of toxicity.
4	61 M	Arteriosclerotic heart disease	Coronary sclerosis myocardial fibrosis	++	215	0.4 mg. daily for 4 days	After 4 days marked nausea and vomiting appeared; dose reduced to 0.1 mg. daily; no toxic symptoms since (1 year).
5	55 M	Arteriosclerotic heart disease	Coronary sclerosis enlarged heart	+	120	0.2 mg. daily	After 3 months pulse went down to 46; reduced to 0.1 mg. daily, no toxic symptoms since.
6	51 M	Arteriosclerotic heart disease	Enlarged heart coronary sclerosis myocardial fibrosis	++++	168	0.6 mg. with repeat in 6 hrs.	After 21 days marked nausea and vomiting; dose reduced to 0.1 mg. daily; no toxic symptoms since.
7	64 M	Arteriosclerotic heart disease	Enlarged heart coronary sclerosis myocardial fibrosis	+	133	0.2 mg. daily	After 12 days bigeminy, drug stopped for 3 days then reduced to 0.1 mg. daily; no toxic symptoms since.
8	67 F	Arteriosclerotic heart disease	Enlarged heart coronary sclerosis myocardial fibrosis	+++	180	0.8 mg. and after 6 hrs. 0.4 mg.	After 58 days marked nausea and vomiting and frequent extrasystoles; drug stopped for 3 days and then reduced to 0.1 mg. daily; no toxic symptoms since.
9	77 F	Hypertensive arteriosclerotic heart disease	Enlarged heart coronary sclerosis myocardial fibrosis	++	170	0.6 mg. with repeat in 6 hrs.	After 14 days diarrhea; drug reduced to 0.1 mg. daily; no toxic symptoms since.

*Maintenance dose 0.2 mg. daily.

Stroud and Vander Veer[78] observed that with digitoxin, the digitalizing dose, when given orally over a period of from 3 to 6 days, was between 1.3 to 2.2 mg. The average maintenance dose was 0.1 mg. daily. Gold et al.[39, 41] demonstrated that a single oral or intravenous dose of 1.2 mg. digitalized the majority of patients, with 0.2 mg. daily for maintenance. Complete digitalization on this schedule was achieved, however, in only about three-fourths of the cases. The maintenance dose, after digitalization, depends upon the individual response. Fifty per cent of patients can be maintained with a daily dose of 0.1 mg.[4] Of the remainder about one-half require more and half require less. One does occasionally encounter a patient who does not tolerate any dose.

It was the impression at the Albany Hospital that there were more cases of poisoning from digitoxin than there had been with the whole-leaf preparations. We, therefore, selected 100 consecutive cases which had been adequately digitalized with digitoxin and had been followed for from 3 months to 2 years. Twenty of these cases developed toxic symptoms. They are presented in the accompanying table. As the cases of digitoxin poisoning demonstrate, they do not differ from poisoning with other types of digitalis. The toxic manifestations did persist longer, however, because of the greater cumulative action of the drug. From our experience, it would seem that considerable caution needs to be exercised in the treatment of patients with congestive heart failure with the digitoxin preparations. Purified glycosides will not result in more efficient or safer digitalization if administered haphazardly.

As has been pointed out by DeGraff, Batterman, and Rose,[18] the response of a patient to digitalis depends upon the degree of congestive failure, the theoretical maximum improvement possible, depending upon the underlying heart disease, and the precipitating cause of heart failure. The dose required for this response cannot be predicted. It varies with the same patient from time to time. Giving an average dose may incompletely digitalize, but far more serious are those cases developing toxic symptoms from the "average dose." Adequate digitalization aims to restore cardiac function as quickly and efficiently as possible. Using the therapeutic response as a guide in giving multiple doses, i.e., 0.4 mg. every 6 hours until the desired effects are attained, one achieves an optimum response more frequently than with either insufficient or over digitalization. Initial digitalization in our experience is best attained with the modified Eggleston method,[19] consisting of multiple doses. Full digitalization is not obtained in most cases when 1.2 mg. are given orally or intravenously in single or divided doses during the initial

24-hour period.[4, 18, 68, 73] DeGraff, Batterman, and Rose[18] have shown that the average therapeutic dose for the multiple dose method is 2.2 mg., as compared with 1.7 mg. for the single undivided dose. Our studies agree with those of Batterman and DeGraff,[4] who demonstrated that the best overall maintenance dose is 0.1 mg. They reported 37.5 per cent toxicity when 0.2 mg. were given daily.

Discussion

There is no question but that digitoxin offers certain advantages. It is a stable, pure chemical, and does not require bio-assay. It is completely absorbed from the gastro-intestinal tract, so that the oral and intravenous doses are the same and interchangeable. The small amount of the drug necessary for digitalization permits administration of a large fraction in a single dose, with only a small incidence of local gastro-intestinal irritation. The rapid onset of action produces quick digitalization by the oral route so that intravenous administration is rarely necessary. There is some evidence that various preparations of digitoxin differ in potency; therefore, as with the whole-leaf digitalis, it is advisable for physicians to use a single preparation with whose action and potency they are familiar. The cost of digitoxin is no longer appreciably greater than that of the whole-leaf digitalis. However, the variability in response to fixed amounts of the drug and the relatively high incidence of toxicity to the generally accepted maintenance dose impose marked limitations on its use. It is probably not the drug of choice for routine digitalization.

Summary and conclusions

1. The history, pharmacology, and toxicity of digitoxin are briefly presented.

2. In a follow-up study of from 3 months to 2 years of 100 consecutive patients in congestive heart failure treated with digitoxin, we have observed toxic symptoms in 20 per cent of the cases. Twenty cases of toxicity are presented briefly.

3. The toxic symptoms appear more frequently with digitoxin than with whole-leaf digitalis, and the toxic manifestations are more prolonged.

4. In most patients 1.2 mg. of digitoxin given in the first 24 hours are not sufficient to achieve adequate digitalization. With adequately digitalized patients 0.2 mg. results in a higher percentage of toxic symp-

toms and for that reason 0.05 or 0.1 mg. is more satisfactory for maintenance.

5. Reasons are presented for selection of the multiple dose method as the one of choice for adequate digitalization.

REFERENCES

1 Apter, L., R. Ashman, and E. Hull: J. Pharmacol. & Exper. Therap., 1944, *82,* 227-38.
2 Arey, L.: Anat. Rec., 1941, *81,* 21-33.
3 Askey, J., and O. Neurath: J. Am. Med. Asso., 1945, *128,* 1016-18.
4 Batterman, R., and A. DeGraff: Am. Heart J., 1947, *34,* 663-73.
5 Batterman, R., O. Rose, and A. DeGraff: Am. Heart J., 1940, *20,* 443-53.
6 Berséus, S.: Acta med. Scandinav., 1943, *145,* 1-76.
7 Blumgart, H., and M. Altschule: Am. J. Med. Sci., 1939, *198,* 455-63.
8 Bodo, R.: J. Physiol., 1928, *64,* 365-87.
9 Boyer, P., and C. Bailey: Arch. Int. Med., 1943, *71,* 529-35.
10 Boyer, P., and C. Poindexter: Am. Heart J., 1940, *20,* 586.
11 Brittingham, H., and P. White: J. Am. Med. Asso., 1922, *79,* 1901-04.
12 Budelmann, G.: Ztschr. f. klin. Med., 1935, *127,* 15-26.
13 Cattell, M., and H. Gold: J. Pharmacol. & Exper. Therap., 1941, *71,* 114-25.
14 Christian, H.: J. Am. Med. Asso., 1933, *100,* 789-92.
15 Cornell Conference on Therapy. Vol. I. Macmillan Co., New York, 1946, pp. 133-51.
16 DeGraff, A.: New York State J. Med., 1946, *46,* 1803.
17 DeGraff, A., and R. Batterman: Med. Clin. North America, 1942, *26,* 929.
18 DeGraff, A., R. Batterman, and O. Rose: J. Am. Med. Asso., 1948, *138,* 475-79.
19 Eggleston, C.: Arch. Int. Med., 1915, *16,* 1.
20 Eichna, L., and H. Taube: Am. Heart J., 1943, *26,* 631-44.
21 Eichna, L., and H. Taube: Am. Heart J., 1944, *27,* 641-56.
22 Eichna, L., H. Taube, and A. DeGraff: J. Pharmacol. & Exper. Therap., 1943, *78,* 22-38.
23 Elderfield, R.: Chem. Rev., 1935, *17,* 187-249.
24 Evans, W.: Brit. Heart J., 1940, *ii,* 51-62.
25 Fahr, G.: Mod. Concepts Card. Dis., 1945, *14,* No. 10.
26 Fahr, G., and M. Buehler: Am. Heart J., 1943, *25,* 211-43.
27 Flaxman, N.: J. Am. Med. Asso., 1942, *119,* 252-55.
28 Flaxman, N.: Am. J. Med. Sci., 1948, *216,* 179-82.
29 Freedberg, A., J. Riseman, and E. Spiegel: Am. Heart J., 1941, *22,* 494-518.
30 Freedberg, A., and P. Zoll: New England J. Med., 1946, *235,* 938-45.
31 Friedman, B., G. Clark, H. Resnik, and T. Harrison: Arch. Int. Med., 1935, *56,* 710-23.
32 Garcia, J., and B. Goldman: Am. Heart J., 1943, *26,* 20-23.
33 Gilbert, N., and G. Fenn: Arch. Int. Med., 1932, *50,* 668-83.
34 Ginsberg, A., O. Stoland, and K. Siler: Am. Heart J., 1938, *16,* 663-74.
35 Gold, H.: Science, 1943, *97,* 125-29; 150-53.
36 Gold, H.: Connecticut Med. J., 1945, *9,* 193-96.
37 Gold, H.: Mod. Concepts Card. Disease, 1945, *14,* No. 11.
38 Gold, H., and N. Kwit: J. Pharmacol. & Exper. Therap., 1940, *68,* 287.
39 Gold, H., N. Kwit, and M. Cattell: J. Pharmacol. & Exper. Therap., 1940, *69,* 177-97.
40 Gold, H., N. Kwit, M. Cattell, and J. Travell: J. Am. Med. Asso., 1942, *119,* 928-32.
41 Gold, H., M. Cattell, W. Modell, N. Kwit, M. Kramer, and W. Zahm: J. Pharmacol. & Exper. Therap., 1944, *82,* 187-95.
42 Gold, H., W. Modell, and H. Otto: Fed. Proc., 1945, *5,* 191.
43 Goodman, L., and A. Gilman: *The Pharmacological Basis of Therapeutics.* Macmillan Co., New York, 1941.
44 Grassman, W., and F. Herzog: Arch. f. exper. Path. u. Pharmakol., 1932, *163,* 97-121.
45 Hatcher, R.: J. Am. Med. Asso., 1920, *75,* 460.
46 Hatcher, R., and J. Brody: Am. J. Pharmacol., 1910, *82,* 360.
47 Herrmann, G., G. Decherd, and W. McKinley: J. Am. Med. Asso., 1944, *126,* 760-62.
48 Jacobs, W.: Physiol. Rev., 1933, *13,* 222-45.

49 Katz, L., and W. Wise: Am. Heart J., 1945, *30,* 125-33.
50 Kininmonth, J.: Quart. J. Med., 1928, *21,* 277-96.
51 Koppe, R.: Arch. f. exper. Path. u. Pharmakol., 1875, *3,* 274-301.
52 LaDue, J., and G. Fahr: Am. Heart J., 1943, *25,* 344-54.
53 Lauter, S., and H. Baumann: Klin. Wchnschr., 1929, *8,* 263.
54 Maresh, G., and A. Farah: Fed. Proc., 1946, *5,* 191.
55 Master, A.: J. Am. Med. Asso., 1948, *137,* 531-34.
56 McMichael, J., and E. Sharpey-Schafer: Brit. Heart J., 1944, *6,* 33-40.
57 McMichael, J., and E. Sharpey-Schafer: Quart. J. Med., 1944, *13,* 123-35.
58 Mies, H.: Ztschr. f. Kreislaufforsch, 1931, *23,* 460-63.
59 Moe, G.: Bull. New England Med. Center, 1943, *5,* 151-54.
60 Moe, G., and M. Vischer: J. Pharmacol. & Exper. Therap., 1938, *64,* 65-85.
61 Movitt, E.: *Digitalis and Other Cardiotonic Drugs.* Oxford Univ. Press, New York, 1946.
62 Nativelle, C.: Moniteur Scientifique, 1867, *9,* 132-43.
63 Nativelle, C.: J. de pharm. et chim., 1869, *9,* 255-62.
64 Nyáry, A.: Arch. f. exper. Path., 1932, *165,* 432.
65 Nylin, G.: Arch. d. mal. du coeur, 1939, *32,* 1010-19.
66 Nylin, G.: Cardiologia, 1943, *7,* 281-303.
67 Otto, H., and H. Gold: Am. Heart J., 1926, *2,* 1.
68 Personal observations.
69 Popper, H.: Klin. Wchnschr., 1931, *10,* 2129-31.
70 Schmiedeberg, O.: Arch. f. exper. Path. u. Pharmakol., 1874, *3,* 16-43.
71 Starr, I., C. Gamble, A. Margolies, J. Donal, N. Joseph, and E. Eagle: J. Clin. Invest., 1937, *11,* 799-823.
72 Stewart, H., and A. Cohn: J. Clin. Invest., 1932, *11,* 917-55.
73 Stewart, H., and A. Newman: Am. Heart J., 1948, *36,* 641-67.
74 Stewart, H., J. Deitrick, N. Crane, and C. Wheeler: Arch. Int. Med., 1938, *62,* 569-92.
75 Stewart, H., W. Evans, H. Brown, and J. Gerjouy: Arch. Int. Med., 1946, *77,* 643-58.
76 Stoll, A.: *The Cardiac Glycosides.* The Pharmaceutical Press, London, 1937.
77 Stone, J.: J. Mt. Sinai Hosp., 1948, *14,* 924-28.
78 Stroud, W., and J. Vander Veer: J. Am. Med. Asso., 1937, *109,* 1808-12.
79 Tandowsky, R., N. Anderson, and J. Vanderventer: Am. Heart J., 1944, *28,* 298-310.
80 Travell, J., and H. Gold: J. Pharmacol. & Exper. Therap., 1941, *72,* 41.
81 Travell, J., H. Gold, and W. Modell: Arch. Int. Med., 1938, *61,* 184-97.
82 Weese, H.: *Digitalis.* George Thieme, Leipzig, 1936.
83 Willius, F.: Med. Clin. North America, 1944, *28,* 905-10.
84 Willius, F.: Mod. Concepts Card. Dis., 1945, *14,* No. 12.
85 Windaus, A., and S. Shak: Ztschr. f. physiol. Chem., 1926, *151,* 86-97.
86 Withering, W.: Med. Classics, 1937, *2,* 305.
87 Wood, P.: Brit. Heart J., 1940, *ii,* 132-40.