that society need not grudge to act to its own advantage because it was also for the advantage of the individual; society did not resent the individual of exceptional abilities but took pride in him. It seems to me that a certain crabbed and ungenerous spirit of envy and resentment against unusual ability is growing; this is underlined by recent events. To me there is something dead wrong with a social philosophy that attempts to set *any* upper limit to the value of the contribution which a man of unusual ability can make to his society, particularly in time of war. In the name of democracy our ideals are becoming less democratic. A partial explanation is doubtless to be found in industrial and capitalistic abuses. But an explanation does not constitute a justification.

We, who are perhaps more vitally concerned than any other group, have thus far failed to take steps to ensure that the economically altered society of the future shall retain those essential features that once inspired our democratic vision. Our conviction has not been strong enough that a society is a good society in which intellectual ability is prized and rewarded. We are passively accepting a change in the economic system by which the relative position of all intellectual workers, including the scientist, is being definitely debased, and in which assurances and commitments made by society in the past are being needlessly scrapped. This applies with particular force to the private universities and to the workers in them. We are not fighting against these things ourselves, and we in the universities are not insisting that our university and educational administrators fight for them for us.

What are we going to do about it? In the first place, we are not going on strike, but those of us who are in the position will continue to work as hard as we can to develop all the devices in the power of our ingenuity or to make what other special contributions we can to destroy totalitarianism and all that it implies. Neither, I think, will scientists attempt to organize themselves into a pressure group to try to mold society to their pattern. Even if it were not ludicrous for so small a minority to think of making such an attempt, we would find such an attempt distasteful at a time when so many of our young men are being called on to make extreme sacrifices. And even if not distasteful, who could find time to devote to such an attempt when we are all so busy with immediate things? But it would be stupid not to take time to at least see what the situation is, and once having seen it, it will be possible to do many things incidentally without slackening in our other efforts. Merely by letting it be known that we are aware of the situation we may accomplish something. From the long range point of view our job is primarily one of education. We should avail ourselves of every opportunity and even go out of our way to make opportunity to let our conviction be known that a society is in the long run the best society in which those who have the ability are given every opportunity and inducement to practice the pursuit of truth and of understanding. We must hold up intellectual power and accomplishment to the admiration and emulation of our young and stimulate their pleasure in intellectual activity. Our educational programs must be revised if necessary to give this emphasis. We must teach our young a social philosophy which recognizes that society is a means and not an end, and we must give them a technique by which they can discover those ends which they can accept with intellectual integrity as making society worth while. If we do not do these things, we are in danger of finding when this struggle is over that we have been fighting for a lifeless husk; if we do them we will be playing our part in molding a public opinion which will create the society of our vision.

DIGITALIS AND SOME OF ITS DERIVATIVES. II

By Dr. HARRY GOLD

DEPARTMENT OF PHARMACOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE

(Continued from page 129)

One of the results of these studies was to show that a similar number of units determined on the frog (U.S.P. XI units) produced widely different effects, while the degree of effect paralleled the number of units determined on the cat. The frog, therefore, appears not to be a suitable animal for the standardization of digitalis preparations that are to be used in man. When the frog and the cat method give different answers in a comparison of specimens of digitalis, that obtained with the cat method is more nearly applicable to humans.

The cat method has now been adopted as the official method of assay in the Twelfth Revision of the U. S. Pharmacopeia. It is to be expected that in the future the potency of digitalis preparations of commerce will be more uniform.

There are certain objections to the cat method as well, since the technique involves intravenous injection, and in that way it fails to distinguish between absorbable and non-absorbable material. This is a matter of some importance, since digitalis is most commonly administered orally in man.

There is abundant reason for the belief that the potency of a specimen of digitalis or a glycoside which is to be used in man should be assayed directly on man.

A method for the assay of digitalis directly on humans has been developed.[21]

Fig. 4 illustrates the technique of an assay in one human subject. The average of a series of such cases represents a complete assay. The essential principles

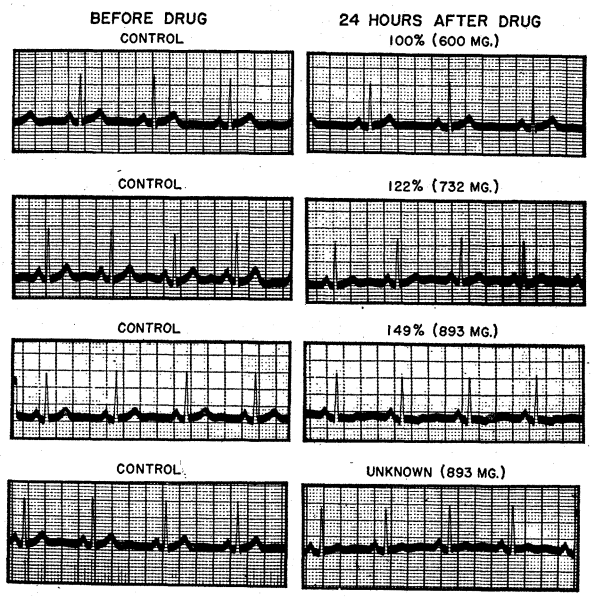

FIG. 4. Assay of digitalis directly on man. Subjects are selected in whom the T-wave is a sensitive indicator of digitalis action. The response of the T-wave is calibrated by graded doses of the standard (U.S.P. Reference Standard) given at one-month intervals. In the above case, T-wave changes clearly differentiate 22 per cent. differences in doses of the standard. Note that 893 mg of the unknown produce an effect between that of 732 and 893 mg of the standard. Hence the unknown has a potency approximating 812 mg or 91 per cent. of the standard.

of bioassay are applied in this method. The sensitivity of the test subject is first determined. A dosage-response curve is established for each case, and the unknown specimen is compared with a standard within the range of the points on this curve.

The reproducibility of results with the human assay, if it is carried out on a properly selected group of human subjects and the technique is followed in all its details, is quite remarkable. We have had an opportunity to assay one specimen of digitalis four times, once in the form of tablets, another time in the form of capsules of the leaf, then in the form of a tincture made from the leaf, and another time in the form of a second tincture made from that leaf. These assays were made on different groups of patients. In humans, the first proved to be 82 per cent. of the potency of the Reference Standard, the second 77.8 per cent., the third 86.9 per cent. and the fourth 77.5 per cent. The average for the four assays of the same specimen indicated that that digitalis was 81 per cent. of the standard, with a maximum deviation from the lowest to the highest figure of less than 10 per cent. Such reliability is not often obtained by animal assay methods.

It is, of course, the hope that one day digitalis materials in general use will be sufficiently pure and constant so that their identity will be ascertained by more precise physical and chemical methods. In that case, we shall dispense with bioassay. But until then the human assay provides the final decision in the matter of the potency of digitalis. To be sure, the human method of assay is not as convenient as the animal methods. The subjects are not as accessible to as many workers. When the importance of human assay is better recognized, however, the apparent disadvantage may be turned to good use in that fewer batches of digitalis may be subjected to assay. The pooling of digitalis into larger units for assay would in itself go a long way toward establishing uniform potency among this group of drugs.

Closely related to the matter of bioassay of digitalis is the problem of digitalis deterioration. After a tincture is stored for about 3 or 4 months it may lose as much as 50 per cent. of its previous potency as revealed by the frog test. But, by the cat test, the tincture usually retains its previous strength. The explanation of this is not clear. It may be that, upon standing, the potent glycosides in the tincture undergo some form of physical change which alters their absorption from the lymph sac of the frog, although in this form it retains its full potency when injected intravenously in cats. Tests with a very old tincture which had "deteriorated" to about one half its strength by the frog method showed full strength in humans. These tests were made by the method illustrated in Fig. 3.

There is considerable controversy concerning the question whether or not the quality of action of different digitalis glycosides is the same. If one material fails to produce satisfactory therapeutic effects, assuming that it has been absorbed and that the dose has been large enough, is it likely that some other preparation of digitalis will accomplish more? That question arises particularly in connection with the treatment of patients in advanced heart failure whose response to digitalis materials is often incomplete or equivocal. From the results of some of the more recent experiments with heart-lung preparations,[22] the conclusion has been drawn that the margin between therapeutic and toxic effects on the heart is much wider for some than for other glycosides. The existing

[21] H. Gold, McK. Cattell, H. L. Otto, N. T. Kwit and M. Kramer, *Jour. Pharmacol. and Exp. Therap.*, 75: 196, 1942.

[22] G. K. Moe and M. B. Visscher, *Jour. Pharmacol. and Exp. Therap.*, 64: 65, 1938.

evidence for this view leaves much to be desired. No significant differences in the margin between toxic and therapeutic doses of a wide variety of digitalis glycosides could be observed in the experiments on the mammalian papillary muscle.[23] The subject has also been studied in man. In these experiments the ratio of therapeutic to toxic dose was measured by the incidence of toxic symptoms when the therapeutic dose was doubled. It was found that with this as a criterion, the spread between the therapeutic and toxic dose for the preparations studied, digitalis, Lanatoside-C and Digitoxin, were substantially the same. The view that strophanthin by intravenous injection produces effects which can not be obtained with digitalis has been popular in the European literature for many years, and has recently been revived in this country. No good evidence exists that this is so, provided suitable measures have been taken to insure that adequate amounts of the glycosides have reached the circulation. We have compared several digitalis materials by intravenous injection, giving the same number of cat units of each in a single dose: ouabain, Lanatoside-C or Cedilanid, Digitoxin and the mixture of glycosides found in digitalis in the form of Digifoline (Ciba). A single injection of 3 cat units of each produces approximately the same result. The effects appear within a matter of minutes, are fully developed within about 1 to 2 hours, and the degree of the effect when fully developed is substantially the same. These experiments were made in patients with auricular fibrillation confined to bed in the hospital, after a long control period, in much the same way as those described in Fig. 3.

One of the most significant pharmacological properties with respect to which digitalis materials show wide differences is that of absorption from the gastrointestinal tract. We have studied this factor in man by the comparison of the amounts necessary to produce the same effect by oral and intravenous administration. all comparisons being made in one and the same subject. The results show that, while digitalis and its tincture are the most absorbable among the crude members of the digitalis group, not more than about one fifth of the potent materials in digitalis plays a part in the therapeutic effects of the drug when administered orally. The rest is chiefly non-absorbable material. An intravenous dose of 3 to 5 cat units produces the same effect as 15 to 20 cat units given orally in the same patient.

The purification of digitalis has often resulted in little improvement in absorption (Fig. 5).[24] The purified principles are in some instances more poorly absorbed than digitalis leaf, as shown by the wide spread between the intravenous and the oral dose necessary for an equal effect. The most outstanding exception is Digitoxin (Digitaline Nativelle). We

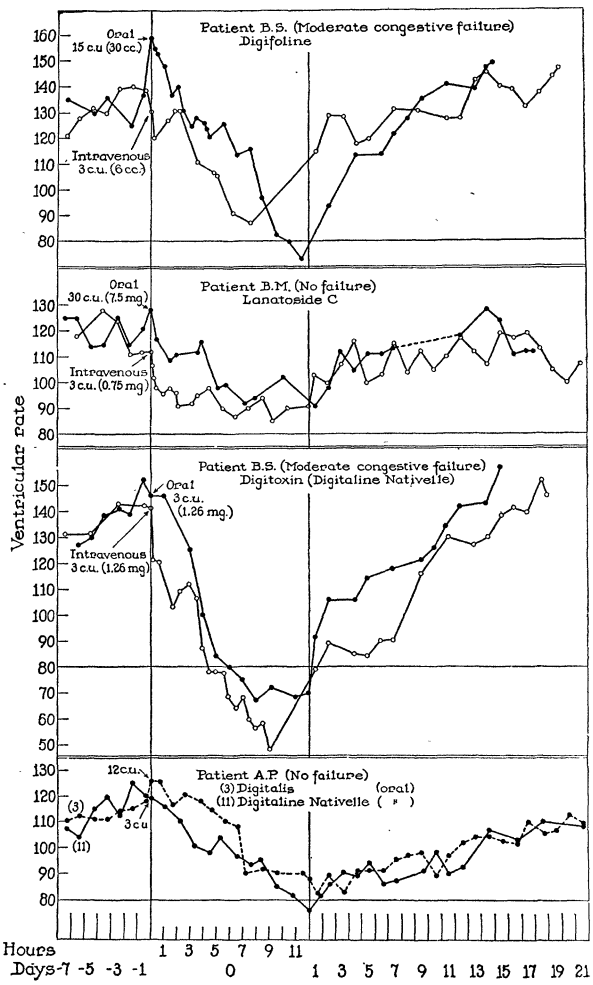

FIG. 5. These patients had auricular fibrillation and were confined to bed. The points on the curves were obtained in the same way as those in Fig. 3. Note that the ratio of oral to intravenous dosage for Digifoline is 5: 1, for Lanatoside-C 10: 1, for Digitoxin 1: 1. Although these ratios vary somewhat from one experiment to another, they represent the usual relationships for these preparations.

have recently subjected this material to more intensive study in animals and man. It possesses a property quite unique for a digitalis body, that of complete absorption from the gastrointestinal tract. A given amount produces the same intensity of effect whether given orally or intravenously. The full digitalizing doses by the two routes in man are practically identical, namely, 1.25 mg or a total of 3 cat units. It is absorbed directly through the wall of the stomach.

These properties have been put to use in an im-

[23] McK. Cattell and H. Gold, *Jour. Pharmacol. and Exp. Therap.*, 71: 114, 1941.

[24] Differences in elimination and destruction within the intestinal tract may play a minor part in the differences attributed to absorption.

proved technique for the treatment of heart failure. In the case of digitalis, it is customary to take a day or two or longer to induce the full effects. The full dose, whatever it is estimated to be, 1 gram or 1.5 grams for a given individual, is divided into 4 or 5 fractions and given at 6- or 8-hour intervals. It is not essential to give it all at one time, since the average patient with heart failure is not *in extremis,* and little is lost by taking 2 or 3 days rather than 6 to 8 hours to induce the full effects. However, the chief reason for the divided doses is the fact that from a single full dose given at one time poisoning may result in the more susceptible individuals. Since varying susceptibility as measured by oral doses includes the factor of varying absorption, it was considered that Digitoxin (Digitaline Nativelle), which is rapidly and, for practical purposes, completely absorbed from the gastrointestinal tract, might provide a means of safe full digitalization by a single dose method. This was found to be the case. The average full digitalizing dose of 3 cat units (1.25 mg) may be given at one time to the patient with heart failure who has not recently received digitalis. It induces the full effects within a period of about 6 hours, sometimes more quickly. With this material there is provided a safe routine procedure of oral digitalization within a few hours rather than in days, as is the case with the customary technique by which digitalis is used.

Digitalis leaf or the tincture can not take the place of Digitoxin in the single dose method of digitalization. A therapeutically equivalent dose represents about 15 cat units, and this causes nausea and/or vomiting in 1 out of every 5 patients within less than two hours, due to a local irritant action, although the local emetic action of digitalis is rarely seen when the full amount is given in a series of small fractions. On the other hand, in the case of Digitoxin, a local emetic action is rarely seen even after the single full digitalizing dose, because the total glycoside for the full effects amounts to only 1.25 mg.

A sharp distinction needs to be drawn between the local and the systemic emetic action of the digitalis bodies. All the digitalis glycosides exert both types of action. We have experiments, however, with various materials such as the glycosides of squill, extracts of digitalis purpurea and of digitalis lanata, and ouabain, which indicate that it requires between 5 and 10 mg of the glycosides, sometimes more, to produce nausea and vomiting by the local action in the gastrointestinal tract. Such an action is therefore to be expected in the case of digitalis materials in which so much of the glycoside is necessary for the full therapeutic effects. It is not likely to occur with those materials of which, by reason of their high potency and completeness of absorption, smaller total amounts of glycosides suffice for full therapeutic effects.

OBITUARY

FRANZ CARL SCHMELKES

1899–1942

HIS colleagues in chemistry, his many friends in the field of medicine and his associates in the industry were shocked to learn of the death of Franz C. Schmelkes. After reiewing his last manuscript he left his office on the evening of December 11, and did not return to his desk the next morning as expected. He had succumbed to a heart attack during the night. This marked the end of a life unusually productive in the realm of science and its industrial applications.

He was born in Prague in 1899, and received his training in organic chemistry at the Carl-Ferdinand University in the same city. He obtained the degree of doctor of philosophy in 1922. For four years he worked in Hanover, Germany, at the Continental Rubber Company and in 1925 he came to the United States. Before joining the staff of the Research Laboratories of Wallace and Tiernan Company, he was associated with the Dovan Chemical Company in Newark, and the Davis Emergency Equipment Company in Hoboken, N. J. For about a decade he had been the assistant director of research of Wallace and Tiernan Products, Inc.

His first major contribution was the synthesis of N,N′-dichloroazodicarbonamidine, a chloramine which is now widely used as a disinfectant. He often referred to this chlorine compound as a "chlorine reservoir" and he felt that its success as a disinfectant is not only due to the slow release of chlorine but also to a quasi-selective action towards bacteria. He and his associates investigated its disinfecting properties extensively, and he collaborated closely with those physicians who used it clinically. His work with this disinfectant brought him in close contact with medicine; and in a short time he acquired an amazing knowledge in all branches of this science. He applied his knowledge of organic chemistry with great ingenuity to problems of therapeutics and usually attacked these problems on a broad front and on the basis of a rather general working hypothesis.

Stimulated by some evidence in the literature indicating that isosteric compounds are similar in their biological activity, he synthesized a group of isosteric compounds and investigated them pharmacologically. One of these was a thiamine analogue; another, a nicotinic acid analogue. Both compounds showed a considerable and specific vitamin activity.