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ILLUSTRATED BY DIGITALIS

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FROM THE
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In the London *Practitioner* for April and May, 1888, there appeared a paper contributed by the writer, entitled "The Primary and Secondary Action of Drugs." It was based upon a somewhat thorough study of the results of experiments on animals by leading German, French, English and American pharmacologists, as well as a considerable clinical experience extending over a period of ten years. In the August number of the *Therapeutic Gazette* of which Professor H. C. Wood is senior Editor, this paper was the subject of a long editorial in which the method and conclusions of the writer were attacked and an attempt made to refute them. The writer replied by contributing to the October number of the same journal an article in which he defended and still further fortified the position assumed. In the same number of the *Gazette* the editors returned to the

attack. Thereupon, the following brief rejoinder was submitted. It was declined with the information that the controversy was closed:

In their first criticism of the theory recently defended by me, that most drugs have a double action, the editors of the *Therapeutic Gazette* conceded that "there are certain drugs which in large doses act in a manner apparently antagonistic to the effects of their smaller doses." In the October number of the *Gazette* they go further and admit that "*many* drugs in small doses appear to act in a method antagonistic to that in which they act in large doses." That is getting on.

The elaborate communication contributed by me to the *Therapeutic Gazette* for October, traversed fully the questions between the editors and myself, and though it was sharply criticized in the same number, not one of the points seems to me to have been really answered.

For rejoinder I might well content myself with begging any reader who is interested in the subject and still in doubt about it, to re-read carefully both the criticism and the communication itself.

There is in the criticism, however, a semblance of reply to my argument in so far as concerns digitalis. The editors in their August number had squarely denied that digitalis even in overdoses can paralyze the heart, and with equal positiveness had

asserted without qualification or exception, that "the heart is arrested in permanent spasm of its muscle [*i. e.*, in systole] by substances of the digitalis group." In the October number I showed that Nothnagel and Rossbach, two of the most celebrated pharmacologists in Europe, had announced as a result of their minute study of the drug—one of the most elaborate and exhaustive to be met with in medical literature—that large doses of digitalis in the case of mammals *do paralyze the heart*, and that so far from being constantly arrested in systole by overdoses, it comes to a standstill finally, *paralyzed in the opposite condition of diastole*.

Contradiction could not be more positive and it comes not from me or any obscure person whose laboratory experiments might be questioned, but from authorities of the highest eminence, practical experts in experimentation on animals, and from physiologists thoroughly trained in laboratory work.

It was shown by me, moreover, that Huchard, another eminent transatlantic expert in the same field, had pointed out that it is only in the case of cold-blooded animals, such as frogs, that digitalis arrests the heart in systole, while in warm-blooded animals, including man, it stops it in diastole. Prof. Lauder Brunton, the most eminent pharmacological authority in England, was quoted against the assertion that the heart is uni-

formly arrested in systole in digitalis poisoning.

Professor Phillips, also of London, and Professors H. C. Wood and Roberts Bartholow of Philadelphia, all noted authors of standard works on *Materia Medica*, were also quoted to show that digitalis affects various parts of the circulatory apparatus in a two-fold manner. They thus aid in clinching the point that the foxglove is no exception to the rule that the small and large doses of active drugs generally have opposite actions.

The citations from these authorities were clear and emphatic to that extent and quite incapable of being misunderstood by any physician of even average attainments.

How do my critics meet all this array of definite and exact testimony? Their answer may be arranged under three heads:

1. They charge me personally (not Nothnagel, Brunton *et al.*) with not being a trained experimenter on animals, and complain because I did not go into the laboratory and illumine the question by taking the cut-out heart of the frog and administering to it various doses of digitalis. If I had rested the case on experiments of my own, such objections might have had force.

2. They try to explain away the statement, cited from Professor Wood's "Therapeutics," to the effect that moderate doses of digitalis cause a strong pulse and high arterial pressure, while poisonous doses cause a weak

pulse and "lowered arterial pressure," so as not to admit antagonism between the different ranges of dose. Their explanation, which is in the nature of an hypothesis, is more ingenious than conclusive. I will not stop now to dissect this hypothesis and show, as can be done, that it is not in accord with the views of most other pharmacologists, and that it is quite insufficient to account for all the facts.

They do not have a word to say about the much more pointed testimony to the double action of digitalis cited from Nothnagel and other celebrated authorities. 3. They acknowledge, however, finally, that "digitalis may sometimes arrest the heart in diastole," notwithstanding that in their first criticism they had unqualifiedly declared that it is "arrested in permanent spasm of its muscle"—*i. e.*, in systole. To break the force of this tardy admission, they now claim that this diastolic arrest is not due to paralysis of the heart but to stimulation of the vagus nerve. How then about the still later stage of the poisoning, in which the vagus nerve itself has been shown to be paralyzed?

To clear up this point it is sufficient to refer the reader again to the lucid and comprehensive statement by Nothnagel and Rossbach of the results of large doses of digitalis, cited at length in my previous communication. These authorities show clearly that while vagus stimulation may

account, in part at least, for the eccentricities of the pulse in the earlier stages of digitalis poisoning, there results paralysis of the heart muscle itself in the final stages of such poisoning, except in the case of frogs, in which death often occurs in systole before the final paralytic effect of the drug has been attained.

Professor H. C. Wood, the distinguished senior Editor of the *Gazette*, has himself, in his "Therapeutics," furnished several pages of testimony pointing unmistakably to the fact that, while in small doses digitalis is, as he phrases it, "a powerful stimulant to the circulatory system," in very large doses it ultimately leads to heart failure and death. However much one may quibble or split hairs in discussing the supposed action of the drug in detail, the great central fact just stated cannot be gainsaid. Other pharmacologists all corroborate it more or less explicitly, however confused and befogged their testimony may sometimes seem to be by detailed accounts of their demonstrations of the supposed action of the drug on various cardiac structures, including the hypothetical nerves, ganglia, etc., which, following Schmiedeberg, physiologists still assume, though the exact functions of these have not been proved. Indeed, Brunton, the ablest and frankest of all the workers in this field, distinctly says in the last edition of his great work on "Therapeutics"—page 314: "Schmiedeberg's hypothetical schema has

been most useful for several years, but facts which it will not explain are beginning to accumulate, and we must look in another direction for their explanation. The whole question of the action of drugs upon the heart is far from being completely solved."

So much for the evidence from the laboratory concerning digitalis. The experimenters agree that it is highly toxic, easily killing when pushed, and not even Professor Wood will ever succeed in proving that it does so in mammals, at least, by making the heart too strong. Clinical experience is all the other way, and shows emphatically that over-dosing with the drug leads ultimately, and often speedily, to cardiac weakness and death from heart failure. Whether it is only the heart muscle or the hypothetical intra-cardiac ganglia which are paralyzed, is not of vastly great importance, considered from the clinical standpoint.

Right here it is in place to say that it is from the clinical standpoint and for the benefit of clinicians and their patients that I am considering this whole subject. It is only in the hope of advancing in some small degree the transcendantly important art of practical medicine that I have consented to make myself a target for personal attacks by championing a somewhat novel view of drug action, and thus demonstrating that there yet lurks, in some conservative corners of our progressive medical profession, a little of that intolerant spirit which Molière so

cleverly satirized by making a candidate for medical honors take an oath never to alter the practice of physic. Yet it has not been intended to say anything not complimentary of the able and earnest men who are engaged in experimenting with drugs upon animals. On the contrary, they are entitled to high praise. Though their results can seldom be received as conclusive till verified at the bedside, very much of their work is distinctly helpful in the direction of advancing therapeutics; and if the theory of the double action were accepted, that large part of the toxicological facts accumulated by them, which, as intimated before, are now comparatively barren and useless to clinicians, could at once be turned to practical account.

The editors of the *Gazette* offer to award me great glory if I will "prove in the laboratory" that digitalis can paralyze heart muscle, and also prove, in the same way, the contrary of various propositions which they lay down. My answer is: 1. That I am not writing up this matter for glory or credit, but for other reasons, as already explained; 2. That other men, who are experts in laboratory work, have demonstrated what is demanded regarding digitalis and have furnished materials, as a result of their experiments, which prove, in my opinion, that all the drugs referred to have double actions.

If the aforesaid editors cannot be con-

vinced by the testimony of eminent authorities in their own special field, they would not believe even one raised from the dead, still less my own testimony, supposing that I could afford to equip a laboratory and find time from a busy practice to make the necessary experiments. If they really doubt that aconitine, veratrine, and viridine have double actions, and will accept as conclusive the experiments of any reputable pharmacologists, I will undertake to furnish the necessary evidence; and in case it should turn out that any of the drugs mentioned has not been sufficiently studied, I will then gladly make additional experiments, either on animals or on men or both, to supply the deficiency. Otherwise it will be quite useless to prolong this controversy. At some future time, however, I may publish numerous reports of clinical cases showing the efficacy of unusually small doses of medicines, administered to antagonize pathological conditions such as could be caused by toxic doses of the same. I hope then to be able to demonstrate at length and with sufficient clearness to convince even the most timid therapist that he need not be deterred, by the fear of treading on heretical ground, from curing his patients with the smallest effective doses, whenever these happen to suit best.

Indeed, one of the most satisfactory things about the theory of the double action of medicines is that it affords an all-sufficient

scientific basis for maintaining that the small-dose effect, as well as the large-dose effect, is really antagonistic to the disease. It thus quite does away with the necessity for lugging in the irrational dogma of *similia similibus curantur* to account for such cures as those of vomiting by drop-doses of wine of ipecacuanha, or of Fowler's solution, and of diarrhœa by fractional parts of a grain of gray powder, rhubarb, or podophyllin. In short, it affords an intelligible and rational explanation of all curative effects obtained with relatively small doses of tissue-disturbing remedies, whether administered by regular physicians or by homœopaths, when the latter do not administer amounts so infinitesimally small as to be incapable of producing any effects.

