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THE CONTINUED AND THE FREQUENT DOSE.¹

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THE systematic treatises on materia medica with which American and foreign medical literature abounds usually give, near the close of their description of the various drugs whose virtues they rehearse, the appropriate dose for therapeutical use, and also the toxicological dose, if the article is capable of exerting any poisonous action on the human economy. Thus Waring, after describing the salts of morphia, adds, "Dose of the morphia salts, gr. $\frac{1}{8}$ – $\frac{1}{4}$ – $\frac{1}{2}$ up to gr. 1."² Stillé concludes his account of the carbonate of lithium with the statement that it "may be administered in doses of from one to five grains three times a day, dissolved in not less than four ounces of water."³ The United States Dispensatory, speaking of the sulphate of quinia, says, "The dose varies exceedingly, according to the circumstances of the patient and the object to be accomplished;"⁴ and then adds that as a simple tonic, a grain may be given three times a day, or more frequently; that in intermittents, from twelve to twenty-four grains may be given between the paroxysms, in divided quantities, according to the condition of the patient and other circumstances. These and similar statements with regard to the doses of medicines, that may be found in all works on materia medica and therapeutics, are essential. They are true as far as they go, but they do not represent the whole truth. They fail to give to the student and practitioner an accurate notion of what an important factor in therapeutics the dose is; and especially do they fail to convey an accurate notion of the therapeutical importance of variation of dose and method of administration.

In saying this, I do not forget that we are told by all works on materia medica that doses should vary with age, sex, temperament,

¹ Read before the Section of Practical Medicine of the American Medical Association, at Louisville, Kentucky, May 4, 1875.

² Practical Therapeutics. American Edition, page 419.

³ Therapeutics and Materia Medica. Fourth Edition, vol. ii. page 351.

⁴ United States Dispensatory. Thirteenth Edition, page 1383.

idiosyncrasy, disease, habit, and the like. This is all true. It has been confirmed by the experience and observation of centuries, but it is not the whole truth. It does not give an adequate notion of the therapeutical power which can be exerted by appropriate physiological doses.

It is the object of this paper to call attention, as briefly as possible, to this therapeutical power, and especially to the action of what, for want of a better designation, may be called the therapeutical action of continued and frequent doses.

Doses of medicines may be appropriately considered under four distinct heads or classes, namely: (1) single doses; (2) continued doses; (3) frequent doses; (4) toxicological doses. The first and last of these, or the single and the toxic dose, are the doses given in treatises on materia medica, and are recognized as representing the therapeutic and poisonous action of any given drug. It is unnecessary to dwell upon them, for they are universally understood. But the bare statement of what is the legitimate single or average toxicological dose of an article like opium, for instance, gives no adequate or intelligent notion of what the continued or frequent dose of the same drug is; nor does it give any adequate or intelligent notion of the physiological action and consequent therapeutical power of its continued or its frequent dose.

Let us consider first the *continued dose*. By this is meant the administration of a drug in such a way that the elimination of one dose shall not be completed before the absorption of the following dose has commenced. "By this method of administration the blood is kept constantly charged with the drug. . . . The difference between the single and the continued dose is the difference between keeping the blood constantly charged with the article administered, and allowing the blood not only to free itself from one dose, before a second dose is administered, but making the intervals between the doses so long that the blood shall be practically a longer period uncharged than charged with it."

"The observance of this difference is important physiologically and therapeutically. The neglect of it explains much of the confusion and discrepancy that may be found in the statements of different observers with regard to the action of drugs. Many of the phenomena, both physiological and toxicological, that follow the exhibition of the continued, do not follow that of the single dose. And, what is in fact a corollary from this, many therapeutical results may be obtained by the continued that cannot be got from the single dose. It is also to be remarked that, although few or no practitioners write as if they were aware of the important difference here referred to, yet the larger number of observations evidently are founded on the action of the continued dose. Physiologists, on the contrary, seem to have experi-

mented oftenest with the single dose.”¹ The continued dose means keeping the blood continuously charged with a medicine by a succession of single doses. The single dose is an appropriate quantity given once or oftener, without keeping it continuously in the blood. The therapeutical value of these doses and the physiological difference between them are of great importance.

Let us look at some illustrations of this difference and value.²

Ammonia and its salts “readily enter the blood, and must to some extent increase its alkaline reaction; but from their volatility and high diffusion power they are rapidly eliminated, and hence their action on the blood and the organs of the body is a very transient one.”³ The elimination of a single dose of carbonate of ammonia is practically completed in an hour or two after it is administered. Its physiological action is correctly stated by the United States Dispensatory to be “stimulant, diaphoretic, anti-spasmodic, powerfully antacid, and in large doses emetic.” In consequence of this action, it is largely used in depressed conditions of the vital powers. This is the well-known action of a single dose or of a few doses given near together, after which the system is freed by elimination from the drug. No change is produced in the quality of the blood. If a continued dose of ammonia is given, that is, if it is given so often, say every hour for several days, that the blood is continuously charged with it, a very different set of phenomena from those just described appear. “When ammonia or its carbonate is administered” — in this way — “for some time to animals or man, the effect is to modify the blood corpuscles; they become easily soluble, crenate at the edge, many-sided, colorless, transparent, collapsed, and loosely agglomerated, but not in rolls; and the blood when drawn, or after death, is absolutely fluid or loosely coagulated.”⁴ These phenomena were observed by Dr. B. W. Richardson, of London. They closely resemble the changes in the blood which occur in patients suffering from typhoid and typhus fevers. Hence it appears that the single dose of ammonia produces rapid and effectual stimulation of the heart,

¹ The Physiological and Therapeutical Action of the Bromide of Potassium and Bromide of Ammonia. By Edward H. Clarke, M. D., and Robert Amory, M. D. Pages 34, 35. These remarks, originally applied to the bromide of potassium, are susceptible of general application.

² In the discussion which followed the reading of this paper, at the meeting of the medical association, several speakers evidently regarded the paper as advocating *persistent* dosing, or *persistence in dosing*, and criticised it accordingly. It scarcely seems necessary to say that the continued dose which is here described has nothing in common with persistent dosing. In order to administer a continued dose of any drug, the practitioner must know and keep in mind the relation of that drug's elimination to its absorption, and be guided by that relation. A persistent doser may persist in giving medicines indefinitely, and never use the continued dose at all. The art of prescribing will never yield its best results till the physiological action of drugs is understood and recognized.

³ A Handbook of Therapeutics. By Sydney Ringer, M. D. English Edition, page 111.

⁴ Practical Therapeutics. By Edward John Waring. American Edition, page 61.

while the continued dose of the same article alters the quality of the blood, and notably of the blood corpuscles. The single dose exerts a therapeutic, the continued dose a toxic action on the economy. It is unnecessary in this presence to dwell upon the obvious therapeutic inferences that follow from these data, at least so far as ammonia is concerned.

Gallic acid is another illustration of the difference between the single and the continued dose. This acid is rapidly eliminated. Physiologists tell us that in a couple of hours after it has been swallowed, it has practically left the system, by way of the kidneys, to such an extent that it exerts no appreciable action upon the blood after that length of time. Gallic acid has a well-deserved reputation for controlling certain forms of hæmorrhage. Suppose it is given in single doses of ten grains, more or less, three times a day, which I apprehend is the usual method of administration, the blood will be subjected to the restraining action of the acid only about six hours out of the twenty-four; not long enough to hold steadily in check a hæmorrhagic disposition. Suppose, now, that instead of the single, the continued dose is administered, by which the ratio of elimination to absorption is constantly regarded, and the blood kept continuously charged with gallic acid; the result will be a continuous action upon the blood, not an intermittent one. It is needless to point out the fact that continuity of action is very sure to give rise to phenomena that will not follow intermittence.

No drug exhibits in a more striking light both the physiological and the therapeutical differences between single and continued doses than alcohol. The partial, confused, and incomplete recognition of these differences by various observers and experimenters, who have examined and described the physiological action of alcohol, goes a great way towards explaining the various and often discordant results at which they have arrived. We learn from the experiments of Messrs. Lallemand, Perrin, and Duroy, as well as from those of Drs. Anstie, Parkes, Smith, Binz, and others, that the disappearance of a single dose of alcohol from the system, either by elimination from it or combustion in it, or by both processes, practically takes place in about six or eight hours after its ingestion. Traces of alcohol may be found in the blood and in the excreta for a much longer period than this; but so much of it leaves the system within eight hours, that what remains of any single dose beyond this length of time has no real physiological value. A person who takes a dose of alcohol, in the shape of wine or other alcoholic liquid, once in each twenty-four hours, subjects his organism to the action of alcohol about one third of that time, and leaves it free from that action about two thirds of the same period. A person who takes what is known in non-scientific language as an "eye-opener" in the morning, wine with his dinner or lunch, a digester in the afternoon, and a

"night-cap" on retiring, takes the continued dose of alcohol. His blood is continuously charged with alcohol to a greater or less degree. There are phthisical patients who imitate this method of ingesting alcohol, and take a daily continued dose of it, keeping their blood charged with it more than two thirds of the time.

Alcohol taken in a single daily dose, by which the blood is practically free from it more than two thirds of the time, and alcohol taken in a daily continued dose, by which the blood is practically charged with it more than two thirds of the time, are substantially different drugs, which produce different physiological phenomena and are or should be employed for different therapeutical ends. This is not the time nor does it fall within the scope of this paper to describe these differences in detail. It is sufficient for my purpose to indicate their existence as illustrations of the single and the continued dose.

The bromide of potassium affords another and most pertinent illustration of the different physiological and therapeutical action which the single and the continued dose of an article may produce. I pointed out these differences in a comparatively recent monograph on the physiological and therapeutical action of the bromide of potassium, and will not repeat them here.¹ Illustrations of single and continued doses, and of the therapeutical importance of recognizing them as factors in the treatment of disease, might be multiplied indefinitely; but enough has been said to call your attention to them and to emphasize their importance. It was impossible to recognize and use them as separate therapeutic factors till physiological observation and experiment had discovered the time and method of the absorption and elimination of drugs, and the ratio of the former to the latter; nor can the practitioner apply them clinically till he knows, at least with approximate accuracy, the way every article he uses gets into and out of the system, the length of time it remains in the system, and its behavior while there.

The administration of medicines to the sick, without regard to the different and often opposite results, physiological or therapeutical, that follow the single and the continued dose, is both unsatisfactory and unscientific. It is unsatisfactory because it fails to secure the legitimate action of medicinal agents. It is unscientific, because it ignores some of the most important physiological conditions upon which scientific therapeutics rest. The time has come for the clinician to recognize and use these and other phenomena of the *modus operandi* of drugs which the physiologist has discovered and whose accuracy he has demonstrated.

Secondly, the *frequent dose* is the giving of a medicine so as to impart to the organism some one or more of its actions, whether primary or secondary, with great rapidity. It is hitting blow after blow in quick succession, upon some organ which it is desirable to affect, in

¹ Op. cit.

accordance with evident indications, with rapidity and power. It is usually, perhaps always, some action of a drug, manifested soon after its absorption, which it is desirable to obtain and which can be obtained by the frequent dose. Obviously the administration of the frequent dose is limited by the physiological behavior of the system under its influence. After a certain period the frequent dose is equivalent to a full single dose or to a toxic one.

The action of opium almost immediately after absorption illustrates the frequent dose. One of the earliest physiological actions of opium after its ingestion, rarely after subcutaneous injection, is stimulation of the nervous system, and of the circulation. This is fully recognized by obstetricians, who advise its exhibition as one means of controlling post partum hæmorrhage. Stimulation is a primary effect of opium that soon passes over, the length of time varying with the quantity given and with the idiosyncrasies of patients, into an opposite condition. The administration of an appropriate quantity of opium every five, ten, or fifteen minutes, that is, the frequent dose of it, will prolong and enhance its primary stimulant action. How desirable it sometimes is to prolong the primary stimulating action of this invaluable agent, I need not remind those who hear me.

The physiological action of aconite upon the human economy illustrates the same principle. Fleming's admirable observations upon aconite have taught us the powerful sedative influence that five drops of the tincture of the root exert upon the system. If, instead of giving five drops in a single dose, half a drop is given every half-hour ten times, or one drop every hour five times, a different physiological and consequently a different therapeutical result is attained from that of the single dose of five drops. In this case a less depressing sedative action is obtained by the frequent than by the single dose.

I will not weary you by these illustrations. I am sure your own observation at the bedside will add to these other and more apposite ones. The object of this paper will be attained if it succeeds in bringing clearly before you the great therapeutical power that results from the physiological adaptation of doses to the processes of absorption and elimination, and especially if it succeeds in calling your attention to the power of the continued dose.