

water, but will rarely, if ever, make one of these surface supplies absolutely safe. For this reason it must be considered as secondary to water purification in preventing water-borne diseases.

5. The use of streams for sewage disposal within permissible bounds is an economic advantage, and absolute prohibition of this use is unjustifiable.

6. This use of streams is sound in principle and safe in practice when proper restrictive control is exercised.

7. The permissible limit of pollution of each river, lake or waterway can be fixed only by careful study of the waterway, and of the uses which must be made of it and to which it is best adapted.

8. Although prevention of all pollution is impossible, control of pollution is feasible and imperatively necessary. The absolute prohibition of discharge of sewage into these waters is scarcely justifiable and the legality of such legislation would be extremely doubtful.

9. The discharge of sewage should be under control and permitted when possible for economic reasons within certain limits. The permissible limit of such reasonable use should be fixed by official standards of the raw water after a careful sanitary survey and consideration of the purposes for which the waterway is necessary or available.

10. These official standards would have to be made for each problem separately and independently, it being manifestly impossible to attempt to fix any general standards of raw water to cover all cases. The acceptance of these basic facts will tend to prevent unjustifiable generalization in a problem in which each city is a law unto itself. By allowing a reasonable use of these interstate waters in the reception of sewage or sewage effluents subject to such restrictions coupled with water purification which will amply protect the public health, the more intensive processes of sewage purification may in many cases be avoided. A city may thus be saved a very great expense which could only be justified on sentimental and not on practical grounds.

To attempt the impossible is not only to court certain failure, but further, such attempts make difficult later efforts of a more conservative and practical nature.

#### ABSTRACT OF DISCUSSION

DR. H. M. BRACKEN, Minneapolis: Some people argue that the purification of sewage should be required to such an extent as to leave the streams into which it is discharged fit for drinking purposes. On the other hand, some engineers go to the other extreme at present, if I understand their position, maintaining that streams are natural sewers, and that they should be used as such, even to the point of creating a nuisance. I think it will have to be admitted that streams must be used for the carriage of sewage; but partial purification of the sewage before its discharge into streams should also be insisted on, so as to make the filtration of the water for domestic use less burdensome.

**Nature's Cold-Storage Plant.**—The markets of Irkutsk, Siberia, are an interesting sight, for the products offered for sale are in most cases frozen. Fish are piled up in stacks like so much cordwood, and meat likewise. All kinds of fowls are similarly frozen and piled up. Some animals brought into the market whole are propped up on their legs and have the appearance of being actually alive. But, stranger yet, even the liquids are frozen solid and sold in blocks. Milk is frozen into a block in this way, and with a string or a stick frozen into and projecting from it. This, it is said, is for the convenience of the purchaser, who is thus enabled to carry his milk by the string or stick handle.—*American Food Journal*.

## A FURTHER RESPONSE TO SOME CRITICISMS OF THE COLLOID-CHEMICAL THEORY OF WATER ABSORPTION BY PROTOPLASM

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A. R. Moore has recently published two articles<sup>1</sup> on edema which are in essence a criticism of some views which I have expressed on this subject.<sup>2</sup> Were it not for the fact that one of these articles has enjoyed a publicity which my efforts have not been able to obtain, it would be needless to publish a response that is a mere repetition of what has been said before and which proves Moore's contentions neither original nor binding.

The facts brought out by Moore in his first paper may be summarized as follows:

When frogs' muscles are placed in Ringer's solution (a mixture of sodium, calcium and potassium chlorid) they do not gain in weight, or they may actually lose. When an "M/8" Ringer solution is used Moore found the muscle to maintain its weight, while when an "M/6" Ringer solution was employed the muscle lost. (It would be of interest to know what Moore means by these abbreviations which mean when written out, respectively, "one-eighth molecular" and "one-sixth molecular" solutions. No chemist could understand these terms as applied to a mixture of three salts, and were he to take Moore at his word the solution prepared would be anything but the Ringer solution known to physiologists.) When varying amounts of lactic acid are added to these solutions Moore found that the muscles did not lose so greatly in weight or that they actually gained. These

1. Moore, A. R.: Can the Presence of Acid Account for the Edema of Living Muscle? Univ. of Cal. Pub. in Physiol., 1912, iv, 111; Fischer's Theory of Edema and Nephritis, THE JOURNAL A. M. A., Aug. 10, 1912, p. 423.

2. Fischer, Martin H.: The Physiology of Alimentation, New York, 1907, pp. 182, 267; The Swelling of Fibrin (with Gertrude Moore), Am. Jour. Physiol., 1907, xx, 330; Further Experiments on the Swelling of Fibrin, Arch. f. d. ges. Physiol. (Pflüger's), 1908, xxv, 90; Analogy Between the Absorption of Water by Fibrin and by Muscle, ibid., 1908, cxiv, 69; The Nature and Cause of Edema, THE JOURNAL A. M. A., Sept. 5, 1908, p. 830; Swelling of Eyes and the Nature of Glaucoma, Preliminary Communication, Arch. f. d. ges. Physiol. (Pflüger's), 1908, cxv, 396; Swelling of Eyes and the Nature of Glaucoma, ibid., 1909, cxvii, 1; Corneal Opacities, ibid., 1909, cxvii, 46; Remarks on a Colloid-Chemical Theory of Hemolysis, Kolloid Ztschr., 1909, v, 146; The Antagonistic Action of Neutral Salts on the Swelling of Fibrin in Acids and Alkalies (with Gertrude Moore), ibid., 1909, v, 197; The Passive Congestion Edemas of Kidney and Liver (with Gertrude Moore), ibid., 1909, v, 280; Edema as a Colloid-Chemical Problem with Remarks on the General Nature of Water Absorption in the Living Organism, Kolloid-chem. Beihfte, 1910, i, 93; Edema: a Study of the Physiology and the Pathology of Water Absorption by the Living Organism, New York, 1910 (also available in German and shortly in Russian); The Treatment of Glaucoma with Subconjunctival Injections of Sodium Citrate (with Hayward G. Thomas), Ann. Ophth., January, 1910; The Nature of Cloudy Swelling, Kolloid Ztschr., 1911, viii, 159; Further Remarks on a Colloid-Chemical Analysis of Nephritis, ibid., 1911, viii, 201; Contributions to a Colloid-Chemical Analysis of Absorption and Secretion (Absorption from the Peritoneal Cavity), Kolloid-chem. Beihfte, 1911, ii, 304 (available in English in Cincinnati Lancet-Clinic, 1912, cvii); Some Practical Points in the Treatment of Nephritis, Ohio State Med. Jour., August, 1911; The Nature, Cause and Relief of Glaucoma, Tr. Am. Acad. Ophth. and Oto-Laryngol., 1911, p. 193; Nephritis: an Experimental and Critical Study of Its Nature, Cause and the Principles of Its Relief, New York, 1912 (available also in German and shortly in Russian); The Contraction of Catgut and the Theory of Muscular Contraction (with William H. Strielmann), Kolloid Ztschr., 1912, x, 65 (available in English in Cincinnati Lancet-Clinic, 1912, cviii, 205); The Absorption of Water by Nerve Tissue (with Martin O. Hooker), Kolloid Ztschr., 1912, x, 283; A Response to Some Criticisms of the Colloid-Chemical Theory of Water Absorption by Protoplasm, Biochem. Bull., 1912, i, 444; The Theory and Practice of Perfusion, Kolloid-chem. Beihfte (with James J. Hogan, 1912, iii, 385; Physical Chemistry in Pharmacology and Therapeutics, Section in F. Forchheimer's "System on Treatment," 1912.

are old facts with which everybody agrees. Their explanation has been frequently given.<sup>3</sup>

Muscle consists, in the main, of protein material. When an acid is added to a protein its capacity for taking up water is greatly increased (it swells). If to the acid any salt is added (even such neutral salts as the chlorids of sodium, potassium and calcium) the swelling is greatly inhibited. The same thing happens in muscle. As soon as muscle is cut out of the body (separated from its blood-supply) it produces abnormal amounts and abnormally strong acids. If such a muscle is laid in water it therefore swells. The addition of more acid from the outside only increases the tendency to swell. If a salt or a mixture of salts is added (Ringer's solution) the swelling is inhibited, and if we add enough salt the muscle can be made to lose water. A "physiologic salt solution" or a "Ringer solution" is nothing but a sodium chlorid solution or a mixture of sodium chlorid with calcium and potassium chlorid (to which some add sodium bicarbonate as in Locke's solution), which, among other things, does not permit skeletal or heart muscle to swell appreciably when removed from the body.

Moore does not believe this. From his three experiments he feels that he is justified in concluding what is by no means new:

It appears . . . that the muscle acts primarily as an osmotic system and secondarily as a colloid.

Moore makes the mistake of not regarding a "physiologic salt solution" or a "Ringer solution" as a man-made mixture which has been found by experimental means to be a better thing than water with which to bathe an excised muscle, but as a divine substitute for blood. Any number of facts show it to be nothing of the kind, but only a solution which, without having any markedly specific poisonous action, counteracts the effect of the acid produced in a muscle removed from its circulation. The laws of osmotic pressure are not being outraged when a muscle removed from its circulation is placed in water, for as long as the muscle is in the body it does not swell even though we drink great quantities of distilled water. Out of the body it swells at once, for no other reason than that out of the body the acid production is greater, so that the colloids acquire a greater hydration capacity. This colloidal swelling is further aided by the fact that in distilled water or in salt solutions of low concentration the muscle loses salt to the fluid in which it lies. In any salt solution, such as Ringer's solution, the acid production in the muscle occurs just the same, but the loss of salts from the muscle is inhibited or prevented altogether, and as there is an antagonism between acids and salts, as we have pointed out repeatedly,<sup>4</sup> the destructive action of the acid on the muscle does not so soon make itself felt in this as in distilled water. The Ringer solution, which Moore regards as "isotonic" with the excised muscle, would be found "hypertonic" if he tried it on the muscle still in the body, for out of the body the acid content runs higher.

In his second paper Moore says:

It has been clearly pointed out by R. Beutner, and I have shown, that if instead the muscles be put into salt solutions, preferably isotonic, to which acid has been added, such muscles first act like osmotic systems and only later like purely colloidal ones.

We are glad to know that Moore agrees half way with us. Beyond this it becomes an ironical fact that Moore should not know that an American, Edward B. Meigs,<sup>5</sup> whose splendid work on muscle has found little recognition here, first raised and tried to answer the osmotic half of the question, on the basis of experimental findings that really have to be met. The subject has been dealt with in detail by William H. Strietmann and myself.<sup>6</sup> Our considerations would seem to indicate that there is no support for believing that any of the phenomena of water absorption in muscle are "osmotic." All the phenomena of contraction, relaxation, tetanus, residual contraction, the staircase, fatigue, etc., can be mimicked point for point by catgut, and the chemical conditions which bring these about are identical with the chemical changes that characterize these phenomena in the living muscle. Further, all the phenomena and the experiments which in muscle are designed to prove its "osmotic" behavior can be mimicked in catgut. Surely Moore would not maintain that several-months-old dry catgut has any "living" osmotic membranes left tucked away within itself.

As a matter of fact, the entire conception of an "osmotic membrane" about cells is an impossibility. An osmotic membrane is a "semipermeable membrane;" it allows a solvent (water) to pass through it, but holds back the dissolved substances. A semipermeable membrane about a cell would therefore permit water to pass in and out according to the laws of osmotic pressure, but no dissolved substances. Oxygen, carbon dioxide, salts and all manner of food metabolites could therefore neither enter nor leave the cell. It is known, of course, that physiologically these substances must do both, so the membranes are said to be "partially permeable." As soon as this is granted, those differences in osmotic concentration no longer exist which make it possible for the water to move; again it is known that physiologically this must also be possible. On the osmotic basis, we may have our choice but we cannot have both.

The colloid-chemical conception of absorption and secretion meets no such obstacles. Water and dissolved substances may here both move, independently of each other, and in the same or opposite directions, governed by the laws of equilibrium and as demanded by the facts of physiology.

Moore continues:

It can easily be shown that acid content does not account for the swelling of muscle in Fischer's "artificial edemas." These edemas are produced by ligating the leg of a frog just above the knee, severing above the ligature and keeping the preparation in distilled water. It was found that these preparations increased in weight. Without attempting to obtain any direct evidence on the point, Fischer lets us assume that this increase in weight is due to the accumulation of acids within the amputated leg. I repeated the experiment and kept the preparations in tap-water for twelve hours. The result in each case was an increase in weight of 20 per cent., as shown in the accompanying table.

#### EXPERIMENT SHOWING EDEMA BY ABSORPTION OF WATER

Preparation	Weight		Increase in Weight, Per Cent.
	At Beginning, Gm.	After 12 Hours, Gm.	
No. 1.....	3.750	4.540	20
No. 2.....	3.805	4.630	20

5. Meigs, Edward B.: *Am. Jour. Physiol.*, 1910, xxvi, 191; *Ztschr. f. allg. Physiol.*, 1908, viii, 81; *Am. Jour. Physiol.*, 1908, xii, 477; *Am. Jour. Physiol.*, 1909, xxxix, 358.

6. Strietmann, William H., and Fischer, Martin H.: *Kolloid Ztschr.*, 1912, x, 65; reprinted in English in *Cincinnati Lancet-Clinic*, 1912, cviii, 205.

3. See the first five references in Footnote 2.

4. Fischer and Moore, G.: *Am. Jour. Physiol.*, 1907, xx, 330, and subsequent papers

At the end of the experiment the preparations were opened and the muscles found to be irritable. When the lymph and muscles were tested with acid fuchsin and neutral red, they were found to be neutral. Clearly, then, acid accumulation does not take place in the artificial edemas which Fischer has devised to prove his hypothesis.

Again Moore agrees with us on certain experimental findings, but the reasoning in the last paragraph is bad. Does Moore wish to go on record as maintaining that any amount of abnormal acid production in a muscle at once does away with its "irritability"? And why should lymph and muscle show an acid reaction to acid fuchsin or neutral red? I have never anywhere maintained that for an edema to develop the tissues had to be acid "in reaction." I have always said that there occurred an abnormal production or accumulation of acid in the tissues. This at times, though not of necessity, becomes sufficient to betray itself to an indicator. As the acid content of a tissue rises the acid combines with the protein (and certain other basic constituents) to form the acid-protein combination which has the greater capacity for holding water; but this acid-protein combination need not have an acid reaction to an indicator, as we have known from biochemical studies<sup>7</sup> on pure proteins since 1895. Clearly then an acid accumulation may take place in these artificial edemas without Moore being able to find it with his indicators. That it does occur has been known for over fifty years and does not depend for proof on any of my experiments. To use only the recent and the best work in this line it is sufficient to cite Fletcher and Hopkins, who found the acid content of the muscle to rise from the first minute of its excision. How then can Moore, with his faulty methods, say that there is no abnormal acid production at the end of twelve hours? As a matter of fact, the most sensitive indicator for acids which we have to-day is the swelling of a hydrophilic protein colloid. K. Schorr and R. Chiari could discover, through the swelling of a protein colloid, the difference in the acid content of ordinary distilled water and the specially distilled water that is used for conductivity experiments in our physicochemical laboratories. Such fine differences have heretofore been demonstrable only by electrical methods.

Moore says in his second paper:

Fischer . . . leaves unanswered the all-important question, Can acid accumulation account for the edema of living muscle?

All my writings on water absorption by the tissues are an answer to this question, though I confess to less skill in differentiating between a "living" and a "dead" muscle than Moore. It would be well for Moore to indicate what criterion he accepts as evidence of "life" in a muscle. On reading Moore's paper one would be led to believe that this is the presence or absence of rigor mortis, or possibly the presence of "irritability." A muscle in rigor mortis is contracted as much as possible, and since ability to contract when touched with electrodes is usually chosen as a sign of its "irritability" (and I do not think Moore used any more refined laboratory method than this), how could this determine whether the muscle was dead or not?

Even disregarding such obvious crudities in Moore's reasoning, acid accumulation can yet account for the edema of "living" muscle. All authors (except Moore) are agreed that the production and accumulation of acid

in any organ runs up from the moment its circulation is interfered with, and if water is available it swells. Yet this organ retains for varying periods and in varying degrees evidences of "life." So a muscle, after removal from the body, and while its acid content is steadily increasing, is still capable of contraction when touched with electrodes, for hours maybe after it is removed from the body, as every one knows. As the acid runs up in the muscle it shows some of the evidences of "fatigue," and if water is available it swells. The slow, stiff, muscular movements of an edematous patient mean the same thing. Even under physiologic conditions a muscle may develop an edema. Whenever a muscle is exercised it produces acid (it is the cause of the contraction), and an active muscle absorbs water in a way that an inactive one does not, as we have known since Ranke's<sup>8</sup> studies.

Moore says:

On the other hand, Kantor and Gies have shown that free acid must be present in a solution in which fibrin threads are suspended in order that such threads may swell.

This statement has been answered several times before,<sup>9</sup> and Gies<sup>10</sup> and I now agree in all essentials.

Again, Moore says:

Von Färth correctly calls attention to the fact that Fischer's colloidal theory of edema seeks to explain only the imbibition of water by the cells, while as a matter of fact the greater part of the fluid of an edema is outside the cells, lying between the tissues.

This argument was originally raised by Felix Marchand and was anticipated and answered in my first writings.<sup>11</sup> The fluid in edema lies both in the cells and between them. But what except water-saturated colloidal material lies between the orthodox cells? Even the mysterious "lymph-spaces" are not holes filled with air but contain water-saturated colloidal material (lymph) which behaves like the more solid material that makes up the cells. All this has been discussed a dozen times.

It is worthy of note that critics like Moore, who, in their own theoretic considerations, could only ignore all that lies between the "osmotic membranes" with which they surround their cells, constantly attack these colloidal-chemical views which alone have been able to explain the behavior of the intercellular tissues and fluids. The intercellular substances, including blood and lymph, behave as do the cells themselves. The water in the intercellular substances, in the blood and in the lymph, is carried as hydration water, just as the water in the cells; and these can be and are given an "edema" under proper circumstances, as truly as any other protein colloidal constituent of protoplasm, be this cell or what not.

Moore continues:

Fischer's later work on "Nephritis" consists of an application of the experiments and arguments used in connection with edema to the more special problems of nephritis, and so criticisms of much the same character as those given on the earlier work apply here.

Briefly stated, the reasons for his theory are three:

1. Fibrin dissolves in acid or in alkaline, but not in neutral solutions, and this, to Fischer's mind, is what takes place in the cells of the nephritic kidney, thus giving rise to albumin in the urine. In order that the analogy may hold, then the secreting cells of the kidney must be acid in reaction.

Not at all. As acid is added to a neutral protein it combines with this, and the acid-protein combination has

7. Sjöquist, J.: *Skand. Arch. f. Physiol.*, 1895, v. 277. Cohnheim, Otto: *Ztschr. f. Biol.*, 1896, xxxiii, 489. Späro, K., and Pömsel, W.: *Ztschr. f. Physiol. Chem.*, 1898, xxvi, 233. Bugarszky, S., and Liebermann, L.: *Arch. f. d. ges. Physiol. (Pflüger's)*, 1898, lxxii, 51. Fischer: *Nephritis*, New York, 1912, p. 23.

8. Ranke: *Tetanus*, Leipzig, 1860.

9. Fischer: *Nephritis*, New York, 1912, p. 184; *Biochem. Bull.*, 1912, i, 452.

10. Gies, William J.: *Biochem. Bull.*, 1912, i, 461.

11. See the first ten references in Footnote 2.

a greater hydration capacity. As the amount of absorbed water rises the protein becomes more and more soft, and finally liquid; that is to say, it goes into solution; but unless an amount of acid has been added beyond the combining capacity of the protein for it, a readily appreciable increase in the number of free hydrogen ions, (on the presence of which an "acid reaction" at all times depends) does not occur. These are elementary facts of modern chemistry.

In stating my second reason, Moore begins:

2. It is shown by means of tables quoted from Höber that urine from nephritides is more acid than that of normal persons.

The combination between protein and acid is still of a disputed character, but in the low concentrations which are alone under discussion, in "living" protoplasm the combination is reversible. In other words, the acid after being put into a protein can be washed out again. If water (urine) is placed in contact with an acidified protein (nephritic kidney protoplasm) the water will have a higher acid concentration (to satisfy the laws of chemical equilibrium) than if the water is placed in contact with a less acid or a neutral protein. Hence, finding the urine of nephritics more acid than normal urine indicates that the protoplasm with which this has been in contact has a higher acid content than the normal kidney. The laws of equilibrium are always the same.

Moore continues:

Farther on in the book Fischer states (p. 184): "The presence of some abnormal acid in the urine does not yet prove that the actual acidity of the body as a whole has risen."

And it does not. To find an abnormal acid is a qualitative discovery, not a quantitative one. The finding of lactic acid in the stomach is the discovery of an abnormal acid there, but it does not prove that the actual acidity of the stomach contents has risen; in fact, in this illustration it means just the reverse, as in carcinoma.

Moore continues:

It is hard to see then how the abnormal acidity of the urine could be used as an argument for the acidity of any part of the body as, for example, the kidneys.

Not if one knows the laws of chemical equilibrium, and will distinguish between the quantitative and the qualitative elements in the discussion as I do in my books and as Moore seems unable to do.

Moore resumes:

3. Artificial albuminuria may be produced in rabbits by the injection of sufficient quantities of tenth-normal hydrochloric acid.

It is curious to note that Fischer goes to great pains to demonstrate that normal kidney tissue is neutral in reaction to acid fuchsin and sodium indigo sulphonate.

It was not necessary for me to demonstrate the neutral reaction of normal tissues and normal body fluids. Fraenkel, Farkas, Höber, etc., did this to perfection years ago. For the rest, Moore twists about one of my arguments which is correct as stated in my book, but not as he states it in the converse. Moore must know that many of our conceptions of the "secretion" of dissolved substances by the kidney depend on certain staining reactions of the kidney substance with acid fuchsin and sodium indigo sulphate. I have merely pointed out that a normal kidney does not stain with these dyes, and by discussing the staining reactions of proteins in the pres-

ence and absence of acid, have insisted that the staining of a kidney with these dyes is evidence of an abnormally high acid content in it. What some of the older authors considered "physiologic" in their experiments, I have therefore taken to be pathologic, and the anuria, the casts and albumin found in these older experiments prove that the kidneys in these animals were not in a "physiologic" condition. But absence of staining does not prove that the acid content of the kidney in any given kidney is not raised above the normal. A certain minimum of free hydrogen ions is necessary before any indicator betrays their presence, and while the hydrogen ion concentration in a kidney may be well beyond the normal concentration, it may not yet be sufficiently high to betray itself to acid fuchsin or similar indicators.

Moore then says of my work:

He then records a large number of experiments in which albuminuria was induced in rabbits by the injection of tenth-normal hydrochloric acid, made isotonic with sodium chlorid solution, but scrupulously avoids telling whether the kidneys in such cases were neutral or acid in reaction.

The injection of acid certainly increased the "acid content" of the body (including the kidney). That is the essential point, and an argument as to whether the kidneys were neutral or acid "in reaction" would add nothing. They might have been either without affecting the argument.

Moore says:

If sections of kidney in a case of artificial nephritis should test acid to indicators we should have good reason for trusting Fischer's theory.

This would contribute to the positive side of the argument, as when a kidney stains with acid fuchsin; but for obvious reasons absence of such findings proves nothing.

To quote still further:

In order to satisfy myself on that point I injected a 2,200-gm. rabbit with 175 c.c. tenth-normal hydrochloric acid made isotonic with serum by the addition of 2.5 mol sodium chlorid. The temperature of the solution was from 35 to 37 C. The injection occupied one hour. One-half hour after the injection had ceased the rabbit was catheterized and the urine found to give an abundant precipitate with phosphotungstic acid. The rabbit was killed by a blow on the head, the kidneys at once removed and sections of them tested for acid with neutral red and acid fuchsin. The result in all cases indicated neutrality of the secreting cells. Occasionally slight staining took place in the lining of the collecting tubes, just as in normal kidney.

Here, then, is a case of albuminuria, induced by acid injection, in which the kidney tissue retains its neutral reaction.

Certainly.

Then Moore says:

If more be needed to indicate the insecure basis on which the acid theory of nephritis rests I might refer to the fact that Fischer himself has shown that injections of solutions of the three sodium salts, sodium chlorid, sodium iodid and sodium bromid, frequently, though not always, cause albuminuria in rabbits. Burnett found that when sea water is made isotonic with blood-serum and injected into rabbits it gives rise to albuminuria.

Large quantities of solution have to be injected, and the lower the concentration of the salt the greater the likelihood of an albuminuria and a generalized edema.

I have explained this finding before.<sup>12</sup> Such large injections are all associated with an abnormal generalized production and accumulation of acid, as is evidenced

12. Fischer: *Edema*, New York, 1910, p. 204.

by the rapid breathing, the fast heart, the cyanosis of the animal, etc.

And yet Fischer advocates to physicians the use of injections of salt solutions in cases of nephritis.

And still does.

If one can, for a moment, forget the skilful and convincing style in which the book is written, and set before oneself the meager evidence which Fischer uses for his theory, the lack of a few fundamental facts at once becomes apparent. . . . He goes on to argue most plausibly that edema in the living animal body is caused by an excessive accumulation of acid. He completely fails to prove that such is the case.

Moore concludes:

It would seem to be wisdom on the part of those engaged in the practice of medicine to view with extreme caution the use of any theory in practice which is founded mainly on argument based on a minimum of experimental evidence. It has been shown how slender is the experimental basis for Fischer's theory of edema and nephritis, and I should say that no matter how skilfully that writer has put his argument, his theory at present has no place in the practice of medicine.

I am constrained to say that it is difficult to answer in good humor such words, which lie well beyond the recognized limits of scientific discussion.

## THE PURPOSE AND LIMITATIONS OF BIO-ASSAY \*

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A century ago, when a physician prescribed, for instance, tincture of opium, he had no way of knowing how much opium his patient would receive save by referring him to some druggist with whose preparations the physician had had previous experience. The evils of this confusion were so apparent that the country had hardly achieved political independence before the medical profession began to agitate for some means of providing uniformity in the materia medica. This agitation culminated in 1820 in the first publication of the first U. S. Pharmacopeia.

Although this work consisted merely of a list of crude drugs with formulas for preparing from them various galenicals, it represented an effort to reach at least an approximate agreement throughout the country in the activity of the commonly used remedies. The sixth revision of the Pharmacopeia, published in 1882, marked another great epoch in the progress toward exactitude in therapeutics, for in this edition was first officially recognized the importance of regulating the quality of the crude drugs from which were to be manufactured the various medicines. There were added, with this in view, not only a description of the appearance of the vegetable drugs, in order that sophistication and adulterations might be the more readily discerned, but also methods for the chemical determination of the percentage of alkaloids in opium and cinchona.

This last innovation was the beginning of an advance in practical therapeutics the importance of which can scarcely be overestimated and an aid for which the medi-

cal profession must forever remain indebted to pharmacy. In the early enthusiasm over chemical assays the professions believed that they had found the panacea which should cure all the evils of uncertainty dosage. It seemed simply a question of time before chemists should discover the active principles of all the potent drugs, and having discovered these, what seemed simpler than to find a means for their quantitative extraction?

Pharmaceutical chemists, especially in this country, attacked the problem with an energy and a determination which would have stormed a Gibraltar. But thirty years of endeavor, while they have greatly extended and perfected the methods of chemical assays, have demonstrated that there are inherent limitations in the art which may perhaps never be overcome.

There is apparently a great group of principles which it is at present impossible to separate in anything approaching completeness or purity. Indeed, up till now the chemical assay has been applied satisfactorily (with one or two exceptions) only to those drugs containing alkaloids, and not to all of these. The U. S. Pharmacopeia VIII, at present official, contains 140 crude vegetable drugs, of which fifty-three are capable of exercising an appreciable effect on the system when given in single dose—that is, are physiologically active. Of these fifty-three only fifteen are officially required to be standardized and it is doubtful if any chemist can satisfactorily test the others. In other words, less than one-third of our potent vegetable drug remedies are susceptible of assay by chemical means. This lack becomes all the more painfully evident when we remember that in the thirty-eight non-assayed drugs are included such powerful substances as lobelia, digitalis, cannabis indica, veratrum, ergot, squills, etc.

The idea of using tests on the lower animals as a means of determining relative therapeutic efficiency seems, like most other important scientific advances, to have been one of gradual growth, so that while many men deserve much credit for their part in its development no one may claim the glory of having been its originator. The thought existed in an embryonic form at least as far back as 1880, but it has reached a conscious, purposeful existence only in the present century. Within the last few years it has been exalted to the position of a fetish; it has been apotheosized by commercial interests and therapeutic incense burned to it as the deliverer from all pharmacologic uncertainties. As one who has been privileged to serve as an acolyte in the temple of this therapeutic deity I thought you might perhaps be willing to listen for a few minutes to what are, in my opinion, the purposes and the limitations of the so-called physiologic assay.

### THE BIO-ASSAY

The underlying principle of physiologic standardization, or as those engaged in this work prefer to call it, the bio-assay, is to determine the quantity of a given sample of drug required to produce some easily recognizable effect on a lower animal. By comparing this with the amount of a standard preparation which will produce the same reaction, one can figure out the relative therapeutic dose. In other words, some physiologic or toxic effect, which may or may not represent a useful therapeutic action, is taken as a criterion of the remedial efficiency of the sample. For instance, in testing digitalis the following method is often employed: Frogs of the same species are carefully weighed and injected with doses of the drug to be tested which are, respectively, smaller, the same and larger than the amount of a stand-

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