find some difficulty in working the tonsil through the small fenestrum, especially if the velar lobe is large, but by systematically pushing the tonsil through from below upward and taking care not to allow it to slip back, or to allow the instrument to be dislodged backward, one will observe, all of a sudden, a giving away of the resistance, and the tonsil is through the fenestrum. The smallness of this fenestrum in my instrument appears to be the first objection to any one not familiar with this method of operating, but I have found that it is preferable to larger sizes, because once the tonsil is worked through, it has a tendency not to slip back and can be snared off more easily.

In connection with this operation, I desire to present two new instruments:

1. Mouth-gag (Fig. 2), which is so constructed as to be always out of the way of the operator. The cross-bars may be turned from one side to the other without disturbing the portion fitting over the teeth. The patient may be placed in any position for operation. It is easy of introduction, and opening, fits jaws or teeth of almost any size or shape, and will not break the teeth or pinch the lips. These are some of the objections to the different mouth-gags on the market.

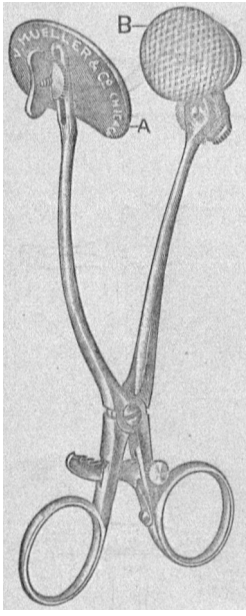

Fig. 3.—Tonsil-clamping hemostat.

2. Tonsil-clamping hemostat (Fig. 3). Should, for some reason or other, bleeding occur either at the time of operation or subsequently, it can always be controlled by this instrument. The inner blade has a cup, into which is drawn a large gauze sponge, and fastened by a thumb-screw. This gauze sponge fits into the cavity created by the operation. The outer blade has at its termination a small oval blade which comes in contact externally with the ramus of the jaw, and acts as the counterpressure for the sponge. It is not painful while applied and will not cause the skin necrosis that one frequently encounters from the older hemostats. The pressure may be regulated by the ratchet lock, and a gauze pad can be placed under the small blade between it and the jaw, thus relieving undue pressure at this point. I have been using this clamp more than two years, frequently placing it in one side while operating on the second tonsil, thus working in a bloodless field. For this purpose, however, since adopting the operation described in this paper, the clamp becomes unnecessary.

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**Natural Feeding.**—Statistics are eloquent in favor of natural feeding. Of 4,000 infants dying in Munich in 1903, 83 per cent. were artificially fed, and in Berlin, in a period of five years, only 9 per cent. of the infant mortality occurred in breast-fed infants. Holt states that, in 1903, of fatal cases due to digestive disturbances in infants, only 3 per cent. had been exclusively breast-fed. As our own Woods Hutchinson tells us: "The best way to modify cow's milk is to pass it through the body of the mother," and "the best and most paying job the community can set the mother at is that of raising her own child to the highest pitch of vigor and efficiency."—C. S. Sheldon in *Bull. Am. Acad. Med.*

## EXPERIMENTAL THERAPEUTICS

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The treatment of every patient is more or less of an experiment. All therapeutics might therefore be termed "experimental"—but there is a vast difference between experiments! Experiments may be framed so loosely, the observations may be so superficial, the analysis of the results so careless, the deductions so illogical, that the experiment has no permanent value—it is not an experiment in the precise sense of the word. A great deal of the therapeutic experimentation of the past has been of this order. However much this sort of therapeutics may or may not help an individual patient, however much or little it may add to the individual experience of the practitioner who practices it, whatever use it may have in one way or another—and doubtless it has some use—it cannot be said to add anything substantial to the stock of human knowledge, to aid others materially in the treatment of their patients, to promote seriously the understanding of the principles of therapeutics.

It is often said—perhaps too often—that therapeutics is not a science, but an applied art. Granting this, is there an applied art which does not rest to some extent on scientific principles, on planned experiments, accurate and reliable observations and logical deductions? The difference between an exact science and an applied art appears to be this: that the applied art involves more or less of unknown, and therefore uncontrolled factors. The master of the art, through intuition or experience, may somewhat discount these uncontrolled factors. But what are "intuition" and "experience" if not a dim perception of the principles involved in the unknown factor? The less hazy the facts, the clearer the judgment. Granting that the day has not come—never will come—when we can reduce all the complicated conditions of health and disease to a mathematical equation—granting that human knowledge has its limitations, here as elsewhere—is this a good reason for "lying down" in inertia, for despairing of all improvement? Because we know that much of therapeutics will never be an exact science, is it necessary or advisable to encourage needlessly slipshod methods?

Empiricism has added much that is valuable to human knowledge—but also much of error. The quarrel of science is not with empiricism as such; the quarrel is with the usual by-products of empiricism: with superficial observation and wild deduction. A *fact* is a fact, whether it is discovered by an academician or by a hod-carrier. If science cannot explain a fact, so much the worse for science—the fact need not care. But science may well afford to be impatient of *pseudo-facts*. It may justly refuse to waste time on assertions which are based on slovenly observations. The man who makes an empirical discovery, who believes it to be a fact, has the moral obligation to establish by exact observation that it *is* a fact, and not a figment of his imagination. If he does not do this, he has no right to speak of it as a fact at all—whether it is a fact or is not a fact, he knows little or nothing about it. Even a lucky guess, even an intelligent guess, cannot pass current in science, is not a real addition to knowledge, until it has been subjected to a fair trial; until it is supported by evidence which is capable of convincing any critical but fair-minded person who is conversant with the subject.

Only then can it be considered as a fact scientifically established. Whether a fact is established or not makes little difference to the fact, but it makes a great difference to science and to humanity. Until a fact is properly established, it cannot be properly used.

The establishment of facts and of the principles which connect them is as useful, as indispensable, in the applied art of therapeutics as it is in any other applied art, or in any "pure" science. Facts and principles can be established only by intelligent and accurate experiments and observations. Hence the need of "experimental therapeutics" of which one hears so much in these days. Experimental therapeutics is not a new science or branch of science; it is nothing more or less than the investigation of therapeutic problems according to the accepted canons of experimentation. Such investigations can be made in a country doctor's practice or in well-equipped hospitals and laboratories—the particular problems might differ, but the spirit would be the same. The essential conditions are not in the material, but in the mental equipment, of the investigator. What is needed is, first of all, a frank dislike for cant—an inability, native or acquired, to accept superficial impressions and hasty conclusions as demonstrated facts. These, for want of something better, may have to do duty in active practice—but even here, they are hazy hints rather than useful tools.

The other requirements are: a problem, a plan to direct observations, accurate records, the comparison, analysis and synthesis of the results and, finally, logical and critical deductions. These requirements exist wherever and however experimental therapeutics is to be investigated.

In detail, the subject may be investigated either at the bedside or in the laboratory; on patients or on animals. Both methods are necessary; each has its peculiar field, its advantages and its drawbacks. There is nothing in the pretended quarrel between the pharmacologist and the clinician, in the pretended struggle for supremacy—nothing but pretense, "clouds of ink and vapors of words."

Pharmacology has for its object the investigation of the action of drugs, and the pharmacologist welcomes any fact bearing on this, with little care whether it comes from the clinic, or from the laboratory, or from the country practice. He welcomes it, whether he can explain it or not, whether it agrees or disagrees with his previous conceptions—provided only that it is a fact—that it bears evidence of being a fact and not an invention of the imagination. The complaint of the pharmacologist is not against clinical therapeutic facts; on the contrary, his complaint is that there are so few of them. He is struck with the paucity of exact, quantitative, critical records as to the effects of drugs on the human individual, either in health or disease. Every clinician has unlimited opportunities for making such observations—he need but stretch forth his hand, blindfold, to grasp a problem, worthy and easy of investigation. With such a wealth of virgin gold lying about uncovered, the pharmacologist—and incidentally also the scientifically trained clinician—cannot be blamed for being somewhat impatient with the counterfeit coinage that is everywhere thrust on him. This is not said in a spirit of fault-finding—all our houses contain some panes of glass.

This, then is one of the most important fields of experimental therapeutics—the carefully planned, accurately executed, and intelligently digested study of the effects of drugs on human patients. This is, of course, the province of the clinical therapeutist. The direct association of the experience of the pharmacologist can, however, be made very useful in this direction, as is shown by the fruits which the suggestions of Cushny are bearing in England. The development of the clinical branch of experimental therapeutics will have an even greater *indirect* influence on the laboratory branch of experimental therapeutics. As has been said, both the clinical and laboratory branches are absolutely necessary for the fruitful development of the subject: the clinical branch, because it furnishes the material, the problems, and the final test; the laboratory branch, because it can furnish a deeper analysis, and therefore a better understanding of the clinical facts. Clinical observations can be made (and to be of any use, they must be made) just as accurate as laboratory observations; but in the human subject, observations cannot be as readily controlled, the conditions cannot be so easily kept uniform or varied—in one word, the problems cannot be analyzed, as they can be in the animal.

The laboratory branch of experimental therapeutics also, is not a new subject. Its essence is nothing more or less than the study of the effects of drugs under abnormal conditions—and almost every analysis of pharmacologic action involves the creation of some abnormal conditions. It is not a new discovery that the action of drugs is modified by the conditions under which they act—this was known before modern pharmacology came into existence. This is merely one of the great but ancient problems of pharmacology, which has of late years received a considerable impetus. Pharmacology has so far concerned itself mainly in analyzing the actions of drugs under relatively simple conditions. As this task advances, the pharmacologist is in a position to vary and to complicate these conditions intelligently, and thus more of his problems come to lie in this special field of experimental therapeutics. This intelligent and planned variation in experimental conditions is at present a very popular subject of research, and deservedly so. It should be heartily welcomed, both by pharmacology and by clinical therapeutics.

Pharmacology, like every science, has its own fundamental problems—problems which often have no immediate practical bearing, though ultimately their practical importance may be all the greater. Like every other fruitful science, however, pharmacology is ever ready to help in the solution of the practical problems of the day. Its principal practical task is to help in the solution of the practical problems of therapeutics. In order that it may help intelligently, the therapeutists must state their problems clearly. As we have seen, this has often not been done, and thereby the usefulness of pharmacology has been greatly diminished, and thereby also misunderstandings have arisen between the more superficial, or more narrow, champions of the two camps. Incriminations and recriminations do not advance us much; the important question is not whether pharmacology or therapeutics shall lead; what leadership is needed, will fall to those who are best able to lead. The important and fruitful question is, how the two subjects can help each other most effectively. And here the cry of the pharmacologists to the clinicians is for problems which *are* problems. Let the clinicians set forth real facts; then the pharmacologist can investigate them and analyze them; he can deduce scientific principles, and even practical hints, which cannot fail to be of direct value to the clinician. When pharmacology and therapeutics do not agree, it means a mistake somewhere: somewhere, the problem has not been clearly stated, the

facts have not been accurately observed, the deductions have not been justified—and often, one can readily see that the mistake begins and ends with the clinician. This does not mean that the pharmacologist is infallible—he is subject to all the human errors of the clinician; but anyone familiar with the literature of both pharmacology and therapeutics can have no doubt as to which is more careful in verifying its "facts," and which, therefore, is more apt to be right.

The error of stretching the deductions beyond the facts may be made by pharmacologists as well as by clinicians. It is a common human failing—which, however, is greatly reduced by habits of accuracy. One particular phase of this is so important, practically, that a few words will be pertinent. I refer to the transfer of laboratory results to clinical practice. Some people affect to look down on experiments with the test-tube, the frog, the guinea-pig, the rabbit or the dog—somewhat as if man enjoyed a peculiar exemption from the laws of Nature. In some instances, this peculiar attitude is due to simple ignorance; in others it is assumed, consciously or unconsciously, from interested motives. These need not concern us. Every scientific worker concedes that there is danger in transferring the experience gained in one field to another field, even when the two fields are very similar. Every caution must be used to make the transfer safe. On the other hand, the progress of science depends on our ability to make such transfers, to "generalize" with judgment. Even medical practice depends entirely on just such transfers—on applying to the new patient the experience gained on the long line of his predecessors. It would be fair to ask where this caution is most often neglected: in the empirical transfer of "practical" experience, or in the critical transfer of laboratory results? The answer is scarcely doubtful.

Here, again, I do not believe that the laboratory pharmacologist is the conceited and dictatorial individual that he has been painted. Do not let us make the mistake of constructing the "ideal pharmacologist" out of our imagination, to meet the fancied needs of debate. Let us take him as he is, as we find him in his own mirror: the special pharmacologic and physiologic journals. If one looks through the papers in a pharmacologic journal without prejudice, one must be impressed by the consideration which is shown to clinical data. In nearly every case, the pharmacologist will seek to correlate his findings with the prevailing clinical opinions. Where he is unable to do this, he may insist that the clinical facts need further investigation or analysis in the light of his results—a fair request, as every one will acknowledge. When he finds that clinicians disagree, he may be pardoned for insisting somewhat on the uniformity and accuracy of his own results—although this may easily be overdone. But it is only when he can confirm and explain the results of the clinic that he speaks with any degree of assurance.

In brief, then, the advance of experimental therapeutics depends on the cooperation of pharmacological and clinical experimentation. The pharmacologist needs to extend his investigations to more varied conditions, so as to discover the basic principles. He is also needed to carry the analysis of the clinical data beyond the limits set by human material. The clinician should both furnish, and finally test, the practical problems. For this, it is essential that clinical experimentation should follow the canons of other scientific experimentation. Otherwise its scientific usefulness is *nil,* and even its practical usefulness is, at best, doubtful.

# THE ACTION OF DRUGS IN PATHOLOGIC CONDITIONS

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The achievements of modern pharmacology may be regarded as twofold in character—scientific, by virtue of its contribution to physiology, and practical, on account of its service to therapeutics. By means of chemical substances we have been able to obtain valuable information concerning the physiologic processes in the lower organisms as well as in higher animals. We have increased our knowledge and broadened our ideas of metabolism in different species of animals, and learned that animals differing widely in structure may yet closely resemble each other physiologically. We have also learned, on the other hand, that important metabolic differences may exist even in forms which are closely allied, and which differ but little or not at all in their mode of living and environment.

The most important achievement, however, of modern pharmacology is its contribution to therapeutics. Not only can we lessen or abolish pain by means of chemical substances, but we are able at present even to eradicate disease. These marvelous practical results are largely due to the study of pharmacologic action and chemical constitution, which is the discovery that the reaction of the cell to a chemical substance may be modified or even completely reversed by a change in one or more elements or radicles of the molecule. The change may be one of substitution of a group, or it may simply be a transposition of a radicle in space. The results of these lines of inquiry suggest that pharmacologic action, which is determined by the interaction of cell and chemical substance, ought to vary whichever constant is modified. A change in the cell may be followed, therefore, by a corresponding difference in its reaction to pharmacodynamic agents.

Evidence is accumulating that any disturbance of the complex and delicately adjusted mechanism of the cell may lead to altered chemical and physical activity. Oxidation may be modified if equilibrium between inorganic ions and protoplasm is disturbed. The permeability of the blood-corpuscles may be altered by altering the physical condition of the colloids, which is likely to be of interest in connection with the mechanism of the penetration of substances into the cell, whatever that mechanism may be, whether physical, as Overton[1] believes for the basic dyes, or chemical, as held by Mathews[2] for these substances, and by Koch[3] for strychnin and other drugs.

Indeed, experimental evidence which has of late years been forthcoming indicates that the reaction of the cell to foreign substances may be quantitatively and even qualitatively different under changed conditions of environment, or after the production of changes morphologic, chemical or physical in character. As will be shown later, a disturbance in any of these factors may bring about corresponding variations in pharmacologic action.

The effects of potassium cyanid on the cell under normal conditions are too well known to need mention. Loeb[4] has shown that the effect on sea-urchin eggs of

1. Overton: Vrtljschr. d. naturf. Gesellsch. in Zurich, 1899, xliv, 88.
2. Mathews: Jour. Pharmacol. and Exper. Therap., 1910, ii, 167.
3. Koch: Jour. Pharmacol. and Exper. Therap., 1910, ii, 265.
4. Loeb: Die chem. Entwickelungs Erregungen des tierischen Eies, Berlin, 1909, p. 53.