

## CURARE: MISCONCEPTIONS REGARDING THE DISCOVERY AND DEVELOPMENT OF THE PRESENT FORM OF THE DRUG

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"Books—to judicious compilers are useful; to particular  
arts and professions, absolutely necessary; to men of real  
science they are tools."

—SAMUEL JOHNSON

THIS dictum of the great lexicographer seems to bear directly upon at least one source of current sciolistic misconceptions regarding the recent development of curare; these errors are found, with unfortunate frequency, in both the scientific and technical literature dealing with the drug, save in the instance of that part written by the medical profession and based upon actual clinical experience with the substance. These papers, almost without exception, are excellent, save for the unconscious absorption of certain misconceptions pertaining to non-medical (e.g. ethnobotanical) aspects of curare. Thus, even a few of the medical articles innocently perpetuate some basic misinformation. Such occurs, however, least frequently among the papers relating to curare's employment as an adjuvant in anesthesia.

It is a curious fact that the basic concept of "arrow-plus-poison" early gave rise to a terminologic scientific misconception in past ages. Ancient classical literature contains many references to arrow poison, the primitive's most effective way of dealing certain death at long range. Homer mentioned it (*Odyssey*, I, 260), as did Horace, Theophrastes, Virgil (*Aeneid*, IX, 772), Ovid (who spoke of arrows smeared with viper blood), and Claudius, when he mentioned the Ethiopian arrow poisons. Even Apollo's darts carried "pestilence," and it is known that the Scythians used animal venom mixed with human blood in the chase of warfare. The subject is also mentioned in the Bible (*Job* 6: 4).

Indeed, our present word forms for poisons and the knowledge and use of them—toxic, toxicant, toxicology, toxicologist, toxin, and so on—are derived from the Greek word *toxon*, meaning "bow," as is the modern term *toxophilite*, which means "a person devoted to archery." Thus, the ancient idea of bows and arrows and poison was fused in a single word concept, symbolized by words of the *tox-* root, and this association of ideas endured for years. It was not until about 60 A.D. that Dioscorides, a physician, first applied the *toxon* concept specifically

to the knowledge of poisons, thus letting the bow-and-arrow part of the original root slide from the colorful glory of primitive battle and hunting into a musty, pedantic oblivion from which it is dragged only by the archery-wise or an occasional sports writer.

Yet there exist today, in some of the most current texts and articles, misconceptions regarding the new curare which appear as scientifically primitive (and with almost as purposive an unawareness of recent findings and concomitant publications) as the *toron* concept of the pre-Dioscoridesians must have seemed to their successors whose basic evaluations and terminology became, at least to that extent, more accurate.

. . . . .

Both immediately prior and subsequent to my (1, 2) final discovery (1938), development, and introduction to the pharmacologic and medical fields of the now accepted, clinically adequate variety of curare, the literature concerning the drug has been augmented very considerably. There are, indeed, not far from 1,000 references thus far amassed for a definitive, multilingual bibliography of curare (3), now in preparation for publication. Owing, therefore, to the extent of the literature, and because the general story, both of early attempts with the drug, and the recent establishment of the clinically adequate variant, has been widely published, it is felt that any lengthy historical resumé of curare would be extraneous to the purposes of this article.

Suffice it to say that although curare—a generic term for various arrow poisons—has been known and used by Indians of South America during and since pre-Columbian times (and civilized nations learned of it as early as 1595 when Sir Walter Raleigh, upon his return from his voyage to the Orinoco, told vividly of use of the poison by the natives), clinical interest in the drug dates back only little more than one hundred years. Watterton and Brodie (1815) demonstrated that asphyxia was the cause of death in curare poisoning, a finding which was confirmed some years later (1844 et seq.) by the French physiologist Claude Bernard (4) who opened the door to all further curare clinical investigation with his discovery of the physiologic action of curare upon the neuromuscular junction.

Brilliant as Bernard's work was, however, and though men like Jousset, Busch, and Demine (1867), Hoffman (1879), Hoch (1894), Cash (1901), Tsocanakis (1924), West (1931-35), Cole (1934), and Burman (5) (1938-39) experimented even further with the drug in various fields, no truly duplicatable or clinically predictable work with the drug was achieved. One factor alone was responsible for this standstill in the scientific and clinical study of the drug: not only were the batches of curare which came out of the jungles to civilization too small for biological standardization, but, and even more unfortunate, rarely were two batches found which were identical in potency and toxicity. That is, the drug, as then known, was not *predictable*.

Predictability is essential in the whole cycle of any drug: in reliable sources, even if these be primitive and jungle-bound; in reliable materials at those sources; in reliable production of a substance which—*en fin*—must be unvarying. The discovering botanist, who is frequently an ethnobotanist; the pharmacognocist, who might be called the liaison officer in the world of drugs; the pharmacologist and the pharmaceutical manufacturer; and, finally, the administering physician—each one bases his work on predictability.

Hence, to make a drug predictable is, axiomatically, to make it functional. If curare could be made predictable in the field of medicine, we decided some years ago, it would offer human values more than offsetting the labor and investment involved in bridging the long and cloudy gap from the primitive jungle to the predictable ampule. That gap, as those of us who participated in the original investigation now realize, was almost inconceivably long and arduous. Our work, both in the field and elsewhere, was necessarily aimed at the objective of a curariform substance which would fulfill, as nearly ideally as possible, those terminal clinical requisites which we had outlined for it in advance. Thus, the most difficult initial labor, embracing some years of sustained field work under jungle conditions before the final expedition of discovery, was to make curare predictable—a complex labor from jungle to laboratory and back again, which was eventually successful to at least a functional, even if not wholly ideal, degree (6).

. . . . .

After the discovery of the new curare, subsequently made available to the profession, work with the drug went forward with pleasing rapidity. Through the untiring efforts of such curare pioneers as Bennett, Cullen, Denhoff and Bradley, Griffith, Knight, McIntyre, Smith, Stewart (7), and numerous others, in the fields of psychiatry, neurology, and latterly, anesthesiology, truly dramatic strides have been made within a few short years since the initial work with the drug was started in this country in 1939.

Yet there are many soundly based indications that this progress, striking as it may seem, is only part of what might be accomplished clinically, if some of the misconceptions relating both to the background of the drug, and also to its current employments, could be cleared up, to some extent, in the literature and in practice.

Ergo, we now face the quite baffling fact that curare's greatest present obstacle is *still* the chimera of *unpredictability*—though no longer of the drug itself. Rather, it is based on a discouraging lack of scientific willingness, in certain nonmedical fields, to acquire, correlate, and then functionally to employ (or, in the instance of publications, to redisseminate) demonstrable and established facts and technic regarding the drug. This unpredictability of *attitude* concerning curare may be found chiefly in (A) scientific misconceptions and literal errors

still extant to a harmful degree in numerous lay, technical, and scientific publications, and (B) an occasional lapse in administration technic—as regards the drug's use as an anesthetic adjuvant in this country—when anesthetic administration is permitted to be performed by other than a physician (8).

In the matter of misconceptions concerning curare, it seems startling that some errors in scientific publications diverge more widely from the demonstrable facts than do many statements in popular detective, and pseudoscientific writings, in whose vivid pages curare—the mysterious and deadly arrow-poison of the jungles—is a frequent, if overly macabre, visitor.

There are still archaic and even dangerous *idées fixes* in the non-lay literature, and, in some instances, scant evidence of the making of all possible use of the "tools" referred to in the opening quotation. This excerpt, ironically, was observed in the front-matter of a text on pharmacology, toxicology, and materia medica (9) published in 1944.

Using this text as an example, since it is typical of several other similar new texts, certain of the statements contained therein seem all the more grave in view of the numerous precedent—and easily available—medical and allied publications (and even awards!) relating to the drug's enthusiastic acceptance as an adjunct in shock-therapy (10) and its introduction as an adjuvant in anesthesia (7).

To quote from the text (p. 403): "The therapeutic use of curare in convulsive conditions of striated muscle has not been encouraged because the dosage is unreliable and because of its tendency to paralyze striated muscle [the basic *raison d'être* of curare!]" If active principles with accurately assayed dosage could be obtained, no doubt curare might be indicated for the treatment of certain conditions of spasm and rigidity of voluntary muscles.

"At present the drug is important only experimentally, for paralyzing skeletal muscles through a selective depression of their nerve endings."

In examining this statement concerning the therapeutic use of curare, we are led to assume that by "curare" the author necessarily refers, in such a recent publication, to the ampuled, clinically adequate curare and not the erstwhile, primitive, crude drug, just as a similar medical reference to the use of quinine would mean, understandably, the drug as prepared for therapeutic purposes and not the raw cinchona bark. If this be so, and assuming his undoubted familiarity with the literature of the past few years, his declaration that the "dosage is unreliable" appears to be an inexplicable misstatement of a scientifically demonstrable fact. The Federally accepted curare, as is available to the profession in ampuled form, is manufactured under constant, clinical control and is unvarying, reliable, and predictable. Further, to commit pharmacologic mayhem upon the drug because of ". . . its tendency to paralyze striated muscle," is analogous to decrying anes-

thesia because it renders a patient insensible to pain! Curare's ability to produce controllable gradients of induced flaccid paralysis of the voluntary musculature is, of course, the fundamental basis for its clinical usefulness in several major and minor fields as a successful relaxant and anticonvulsant.

It is also interesting to note that this text, published in 1944, gives no reference later than 1927 in its historical data on curare, a fact which lends a certain aura of dubiety to the selection of the quotation from Samuel Johnson as part of the book's prefacing matter.

As examples of an additional category of misconceptions, we find that another widely used manual of pharmacology (11) reports that curare is ". . . prepared from the root bark of several *Strychnos* plants . . ."; a prominent Index (12) of pharmaceuticals describes curare as ". . . an extract from the bark of various species of *Strychnos* . . ."; and the U. S. Pharmacopoeia, in its 12th revision (13), states; "Different specimens [of curare] vary, depending upon the variety of plant used in its manufacture. The most important source of curare is the bark of several species of *Strychnos*. . . ." Numerous other lay and medical dictionaries and texts contain similarly inaccurate or incomplete definitions.

Still another text (14), apparently a bit enmeshed in its autogenous ethnobotanical concepts, states in one paragraph (p. 495) that "the drug is an extract of the barks (*sic*) of . . . *Strychnos* plants." Yet in the immediately succeeding paragraph it affirms that "curare is obtained by brewing the stems, roots, bark, and leaves . . . of *Strychnos*" . . . certainly an all-inclusive extraction!

Thus far, as we have seen, the authorial conjectures and odds have been placed squarely upon the not too ample phytogenous shoulders of the long-suffering *Strychnos*\* group (fam. Loganiaceae). There is, however, another school of thought in equally current texts, manuals, and commercially distributed technical bulletins which implies a similar ethnobotanical "monopoly" for curare in the family Menispermaceae, especially in the *Chondrodendron* species. One such publication,† for

\* NOTE: The fundamental correctness of this generic name as applied to this group (*Strychnos*) of curare plants, incidentally, has been a matter of botanical taxonomical argument for several generations, since Schomburgk first named a curare species thereunder (c. 1844).

† NOTE: As a matter of further interest, several of these commercial technical publications (and, indeed, quite a few of the articles by "scientific writers" in the major popular magazines) furnish an instance of a frequently published historical error relating to the advent of the present form of the drug. This error, in essence, consists in placing the terminal discovery of the clinically adequate curare some five years ahead of the actual date (1938) and implying, thus, an extra half decade of "laboratory research" before the drug was presented to the profession. These, and similar publications, also claim commercially-based financial, and other, sponsorship for the discovery and evaluation of the drug. Factually, the work was undertaken entirely privately, with neither commercial sponsorship, connections, nor even encouragement. It was only after the pioneering pharmacologic and clinical endeavors were already instituted at the University of Nebraska that the drug was first released to a commercial firm, under the aegis of attested documents, in July, 1939. Thereafter, it was released commercially, for purposes of clinical experimentation, to the profession. Later it was placed on general pharmaceutical sale with the acquiring of Federal acceptance.

example, taking up an unsound pharmacognostic cudgel in favor of *Chondodendron tomentosum*, alleges, as of 1945, that all curare (primitive, and otherwise) is made solely from the bark and stems of *that* particular species . . . thus constituting one of the most flagrant errors, of this category, in the literature.

That these ethnobotanical and pharmacognostic concepts are entirely misleading (and obviously incommensurate with any reasonable survey of the curare literature) may be judged readily when one considers that: all types of curare, both primitive and evolved, most often studied for whatever reason during the past decades—not only by others but by the author—have each contained a complex of botanical ingredients (some even with the gratuitous addition of primitive “biologicals”!) variously grouped, from:—A—(of primary importance) Loganiaceae (*Strychnos* spp.); Menispermaceae (*Chondodendron*, *Cissampelos*, *Sciadotenia*, *Telitoxieum*, *Elissarrhena*, *Anomospermum* spp., etc.) and—B—(of secondary, and even rare use) Piperaceae (*Piper* spp.); Annonaceae (*Annona*); Leguminosae (*Lonchocarpus*); Rutaceae (*Erythrochiton*); Moraceae (*Ficus*); Rubiaceae (*Psychotria*); Solanaceae (*Capsicum*); Aristolochiaceae (*Aristolochia* spp.) (15, 16).

It may be superfluous to remark that all of these plants, or ingredients, represent officially authenticated and published (16) botanical collections of long standing and by various collectors, in many herbaria here and abroad. My own collections are deposited in the New York Botanical Garden, the Arnold Arboretum (Harvard), and are referable elsewhere. For this reason, I feel it entirely allowable, and even necessary, to publish a definitive statement that the clinically adequate curare for whose introduction I am responsible, originated in a qualitatively and quantitatively formalized complex of botanical ingredients, and not in any single species, or single genus, or even single family of plants. Indeed, contrary to the U. S. Pharmacopoeia (13) (“Curare—The composition of curare is not definitely known”), the composition of the drug, in its present form, is definitely known!

Even regional errors relating to the geographical distribution of curare are fairly numerous. These, in the main, tend to “monopolize” certain regions of the American tropics in much the same manner, as we have seen, that different plant species or genera are given the sole credit for supplying any or all kinds of curare. One instance will suffice for this particular category of misstatement. A popular pharmaceutical Index (12) sums up the entire ethnogeography of the drug on the following somewhat circumscribed basis: *Habit.* Orinoco, S. America. It is the arrow-poison of the Orinoco Indians.” Factually, primitive curare under its variant names (curari, wourara, wourari, wourali, urari, curara, urirarery, etc.) is widely distributed throughout northern and western South America (1, 16) in those climatic zones amenable to the growth of a sufficient quantity of its component botani-

cals, the Orinoco Basin being one of the sources of the material, but far less productive than other and larger regions of Amazonian drainage.

However, in all this seeming welter of misinformation and factual obsolescence, one major misconception, almost above all others, persistently keeps forging its regrettable, but doughty, way through the various publications which sustain it. One quotation from a textbook of pharmacology (11) will serve to illustrate this widely appearing error: "The varieties [of curare] are designated by the kind of containers in which they reach commerce: *Calabash (Gourd) curare* is obtained principally from *Strychnos toxifera* and contains curarine. *Tubo curare*, in bamboo tubes, is of undetermined source and contains tubocurarine and curine. It is the least desirable but the most common variety. *Pot or jar (Topf) curare* comes from *Strychnos Castelnaei* and *Cocculus toxifera*, and contains protocurarine and protocurine."

This idea occurs in other references too numerous to mention and has, in fact, been innocently repeated in medical articles of recent date.

Factually, the type of native container in which primitive curares made their precarious way (usually via trader) to civilization is in no way a reliable, and certainly not a scientific, indication of the "kind" of curare contained therein. Indeed, the type of container—bamboo tube, small clay pot or jar, dried gourd, etc.—depends entirely upon which comes first to the hand of the Indian maker, and which coincides most nearly with his jungle-bound whim of the moment. Least of all does the type of primitive container indicate the species of the ingredients in the curare it holds. Primitively, these vary from region to region and from day to day, depending upon the season of the year, the materials at hand, the area, and above all, upon the ritualistic witchcraft vagaries of the maker—whereby he is prompted into adding to his brew almost anything available in the entire jungle, whether of animal or vegetable origin, which he fondly hopes will prove lethal! Consequently, to attempt to define any kind of curare by its container and, additionally, to assert that this "kind of curare" is prepared principally from some one plant, is a scientific error of considerable magnitude.

Indeed, this error has been an all but fatal obstacle in curare studies (17) made previous to the evolution of the present clinical form of the drug, and to certain ones thereafter, in which primitive curare was used. Much of the value of these studies (both in the ethnobotany and the alkaloidal chemistry of the drug) has become negated because the work was done on small amounts of heterogeneous mixtures brought into civilization by wanderers in the South American wilderness, who obtained the gourds (or bamboo tubes, or clay jars, or whatever) of the material without in the least knowing either quantitatively or qualitatively what had entered into the mass. No field authentication was made of the botanical ingredients or the proportion used in these

batches of curare, and therefore no predictable duplication could be made of those batches on which many detailed and exhaustive fractional analyses were based. As a consequence, and until very recently, curare was, therefore, "scientifically classified" by the *type of container* in which it happened to make its first appearance in civilization. Thus was achieved the unhappy terminology of "pot-curare," "gourd-curare," "tube-curare," "tubo-curarine," etc.—as futile a system, scientifically, as endeavoring, for example, to classify quinine salts by variously calling them pasteboard-box-quinine, or glass-vial-quinine, or, possibly, bakelite-top-bottle-quinine (6).

Still other categories of scientific error and misconception continue to appear and—as is apparently the classical beginning of any new drug—will doubtless be repeated for some time to come. These categories relate especially to the pharmacodynamics of the substance and its physiologic actions. Fortunately, many of these seem about to disappear, in the light of curare's relation to the current, admirable concepts of neurochemical transmission (18), and the substance's probable effects upon the higher central nervous system, including its recently recorded suppressor-inhibitor action upon the cortical potential (19), matters of future importance (especially in anesthesiology) which it is not the purpose of this article to mention further than in passing.

So much, then, for one major grouping of the unpredictable obstacles which the now predictable curare still faces. The other major unpredictable obstacle—and danger—for the drug, as mentioned earlier, lies in the administration of curare in anesthesia by nonmedical anesthetists, especially in this country. It is the definite consensus of my medical confrères (8) that the administration of curare (and the judicious handling of the curarized patient) is at least, and possibly more so, as grave and responsible an incursion into that field legally defined as the "practice of medicine," as is the administration of any anesthetic agent *per se*.

It were too great a waste of a clinical tool of such high potential value that it should come to grief in other than adequate medical hands. We therefore feel with Dr. Oliver Wendell Holmes (20): ". . . if it can be shown that . . . lives have been and are sacrificed to ignorance or blindness on this point no other error . . . will be alleged in palliation of this; but that, whenever and wherever they [technicians] can be shown to carry . . . death instead of health and safety, the common instincts of humanity will silence every attempt to explain away their responsibility . . ." . . . in which excerpt we beg that the concept of curare's nonmedical administration in anesthesia be substituted.

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