AMPULS.

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THE EVOLUTION OF THE WORD "AMPUL OR AMPOULE."

The newer Pharmacopœias have been practically enforced to give ampuls a place by the always evident Pharmacopœia elegans, inasmuch as ampuls have lately come into extensive use.

The etymological origin of the word "ampul" in English, or "ampoule" in French, is not absolutely clear. There are two possibilities. It may have been derived from a diminutive of a Greek word "amphora," or from a lost Latin word "ambolla," compounded from "amb-olla." But the Latin and Greek languages are offsprings of an older mother language, supposedly the Indo-Germanian language. If we trace either "amphora" or "ambolla" to their original shape in the presumed Indo-Germanian language, we will find the same ideas prevalent. "Amphi" in Greek and "ambo" in Latin, mean the same and lead to the idea of a vessel having a handle on each side.

In German the development of the word "Zuber" is the same. "Eimer," from "ein-ber," meaning one handle, and "zuber," from "zwei-ber," meaning two handles, designate different vessels bearing one handle, or others bearing two handles. It is clear that originally the vessels called "amphora," needing two handles, must have been very large, and indeed they were.

We find such vessels corresponding to the denominations "amphora," in old Egyptian pictures, in excavations of Schliemann of Troy, and in some pictures and excavations of old Greece and Rome.

In some instances, this "amphora" had a standard capacity. In olden Greek times, this "amphora" had a capacity between eight and a half and nine gallons. In the later time of the Roman Empire this capacity was decreased to only six gallons.

Besides these enormous vessels, there were also small oil containers used for illuminating purposes, having chains attached to them on both sides, as parts of candelabra. These small oil lamps had two handles attached for the bearing of chains or strings, and were also called "ampulla," and therefrom originated the small hanging lamps called "ampels," which are still used in Germany, Holland, Sweden and Norway.

This word "ampul" was known two thousand years ago, as a rare word in the old Latin language, and it became more frequently used in mediæval Latin of the Catholic Church and in Medicine.

Large vessels gradually assumed a special shape. The possibility of these vessels carrying large amounts of a liquid led to a belly-shaped vessel. The possibilities of contamination by contact with the air, evaporation or spoiling while pouring out the liquid from large orifices of these belly-shaped vessels led to the construction or rather the formation of vessels having narrow necks.

Henceforth, a large vessel, flask-shaped or belly-shaped, having a long thin neck, with no handles, was the only remaining form prevalent and all other forms

and shapes were forgotten. The first perception can be traced back two thousand years ago, whence the adjective "ampullaceus," and not "ampulla," applied or rather designated a vessel as above described.

Plinius used this adjective "ampullaceus" to designate a pear which was belly- or flask-shaped, having a thick or rather broad belly and a long thin neck. During mediæval times the pilgrims to the Holy Land used to carry water contained in flasks made from pumpkins, having the above described shape. The older shape, namely, having two handles attached to the "ampul," was lost in mediæval times for the word "ampulla" itself.

From now on, the ampul assumed the shape of a container having a large belly and a small neck, which was made from different kinds of colored glass and even earthenware and leather, and later on of pumpkin skin.

In the Latin of the Catholic Church, we find small "ampulla" holding holy oils or blood of martyrs. In Canterbury and Rheims there were "ampuls" containing holy oil used for crowning the Kings of England and France.

In the Roman Church, they have "ampuls" containing wine and water for use in mass, and others containing oils were used for different sacraments.

In Scientific Botany and Biology the word "ampulla" is often used, which in Morphology designates flask-shaped cavities.

In French "ampoulette," Dutch and Swedish "ampulette," refers to a vessel which does not have handles on both sides. It refers or rather designates a vessel, bulbed or rather bellyed at each end and connected by a long thin neck, through which ran sand at certain time intervals, as for example, a quarter of an hour or half an hour, and which was called an hour-glass. The sand was placed in one end of the vessel and as it ran through the neck into the other vessel, it would thereby designate the time. When all the sand ran into one vessel, it was then inverted and in this way they used to differentiate the hour, or rather the time of the day.

In modern times the word is still used in some Romanic languages; but in these languages the word has partly a "u" and partly an "o" as the original "amphora" or "ambolla."

"Ampulla," or the respective derivative word of these modern languages, means a flask, bottle, jar, pot or other vessel swelling in the middle and furnished with two handles.

The latest development was to use the word "ampoule," originating in France, designating some kind of little flasks of glass with long necks and closed or rather sealed by the gas flame and enclosing volatile liquids for chemical purposes. From these ampoules the pharmaceutical "ampoules" have been derived. In English and German this word is generally written "ampul."

DISCUSSION.

Among the noteworthy advancements in the preparation of medicinal agents, the ampul has attained a very useful position. It has made it possible to administer with celerity, accurate amounts of sterile solutions, of definite strength and known therapeutic value. These solutions are injected subcutaneously, intramuscularly or intravenously, but rarely by other methods of administration, as for example, ethyl chloride. The field of administration of such injections

has greatly increased because they are rapidly absorbed, while certain of them are delivered directly into the circulation. Therefore much loss of time and imperfect absorption of the medicinal agent and waste is avoided. Furthermore, gastric intolerance to certain drugs or serious tax upon the digestive organs may be mostly eliminated. Convenience and safety are the keynotes of ampul therapy, while quickness and directness of action are features deserving scarcely less emphasis. To date, no container has proven as practical as the ampul, which for evident reasons has become immensely popular with physicians.

HISTORY OF MEDICINAL AMPULS.

G. Pegurier says that the first ampuls were Pasteur's pipette and the sterile flask, which were suggested in the course of his researches on bacteria by a desire to obtain pure cultures by using an absolutely sterile medium and to preserve these cultures from accidental contamination by extraneous organisms.

It was about thirty years ago, that Limousin, a French pharmacist, proposed the ampul as a convenient method of preserving hypodermic solutions, while a paper describing ampuls was published in the "Bulletin Generale" of the "Societe de Therapeutique" for April, 1886.

In foreign countries, especially in France, this method of dispensing has attained its greatest popularity. In 1905 in a great many Russian pharmacies, ampules were filled by use of the hypodermic syringe or by heating and dispensed on prescriptions.

The French have made a very general use of this form of medication which is as popular in the Latin countries of Europe as the hypodermic tablet is in the United States. In time the hypodermic tablet will give way in popularity to the ampul for general use in the United States. As a matter of fact the principal danger of infection in the use of ordinary hypodermic injections comes not from the solution but from the syringe of the physician, who does not use sufficient care in sterilizing it before putting it into use.

FORMS OF AMPULS.

The largest ampuls on the market are the ethyl chloride ampuls. Ampuls vary greatly in capacity; large ampuls being used for massive injections of saline solutions. The form varies as widely as the capacity. The original form proposed by Limousin consisted of a round bulb with a neck drawn out to a small tube, therefore the name ampul, as explained in my introductory chapter. The dropper ampul has been introduced by many large manufacturers for dispensing chloroform. The tubes of concentrated spirit of nitrous ether and those of ethyl-chloride are also put up in ampul form which were originated by Bengué. A special form of ampul which can be used as a hypodermic syringe called the "Omnium Ampoule," is of French origin and is now also made by American manufacturers.

MANUFACTURING OF AMPULS.

Glass Required for Ampuls.

Tending to cover such a wide scope of uses, the ready ampuls must be fit for all kinds of fillings. The best glass that can be used for such ampuls is a neutral glass, that known as Jena Normal 16 III or that termed Fiolax glass, white or

amber, as ordinary glass contains soluble alkali, which affects the solutions therein contained. For example, ordinary glass will precipitate crystals of strychnine which may be small enough to pass through a hypodermic needle and cause great pain when injected into the tissues. For solutions which are changed by the action of the light, as ferric solutions, apomorphine or physostigmine solutions, ampuls of amber glass should be employed.

GLASS TESTS.

A good method to try out the glass is to fill the ampuls with a one percent alcoholic solution of phenolphthalein and boil them for about half an hour. If the solution yields a pinkish color, then the ampuls should be rejected.

In order to test for the presence of the soluble modification of silicic acid, place some of the ampuls in one hundred cubic centimeters of tenth normal potassium hydroxide solution and boil for one hour. Then concentrate it down to ten cubic centimeters. Then let it stand for twenty-four hours and if a turbid precipitate of silicic acid is formd, the ampuls should be rejected on account of the presence of free soluble silicic acid.

The Swiss Pharmacopœia directs that the empty ampuls should be rinsed with dilute hydrochloric acid, followed by distilled water with the idea of neutralizing excess of alkali.

If the ampuls are cleaned one day with hydrochloric acid, they should be washed well and cleaned for twenty-four hours with an alkali or better still, inverted, clean first with alkali and the second day with acid.

THE MAKING OF THE EMPTY AMPULS.

The manufacture of empty ampuls has developed into a special business both in Paris and in Thuringia, Germany. Among the leading manufacturers of the empty ampuls are Adrain and Fournier of Paris, and Fridolin Grenier of Neuhaus am Rennweg, near Jena, Germany. Where the dispenser is unable to purchase the ready-made ampuls, he can make them himself, from Jena glass tubing, if only ordinarily skillful in glass blowing.

With a little care, it is very easy to make ampuls for your own special use. Take a small Jena glass tube about half an inch in diameter. Close it at one end by heating it in a blast or an ordinary bunsen flame. Heat it again, this time further up, until it becomes soft and with a gentle pull and twist, an ampul can be made, which is as good as that made by any manufacturer.

By blowing a current of air into the side of the heated ampul, a spout is formed which is very useful for keeping and pouring out liquids. Such ampuls can be used for keeping chloroform, ergot, digitalis and strophanthus solutions. From the above, we can see that there is really no excuse for anybody saying that ampuls cannot be made because the empty ampuls are hard to obtain. With just a little tact and manipulation, one can make hundreds of ampuls within a short time.

CLEANING THE EMPTY AMPULS.

Place the empty ampuls into a suitable vessel of distilled water, bring to a boil, remove the flame and pour cold distilled water on the ampuls as they float in the boiling water. They at once fill themselves. Again bring to a boil, when all or nearly all the water will again be expelled. Then sterilize in an oven at 120° C.

METHODS OF FILLING AMPULS.

The methods of filling ampuls may be divided into three classes:

1. By Gravity. 2. By Pressure. 3. By Vacuum.

Under each of the above headings, a description of the working of one instrument will be given in full, which will in all probability apply to all instruments, although differently constructed, yet working upon the same principles.

Every ampul to be filled must have a larger capacity than the contents therein to be placed. This is on account of sealing, because it is absolutely impossible to seal the neck of the ampul in the flame if the point and surrounding neighborhood is not absolutely dry, because wet glass in the flame cracks.

BY GRAVITY.

A very simple form of gravity filler and one easily understood is a burette. As the burette is accurately graduated, it makes it very easy to measure the amount of solution put into each ampul. As the opening of the burette is quite large, compared to that of the ampul, all that is necessary to do, is either to close the opening of the burette a little by the aid of heat or else attach a piece of rubber tubing to it, having attached at one end a small glass tube.

All that is necessary to do, is to pour the sterilized solution into the burette and cover the top of it, so as to prevent any contamination of the solution. Then by placing the ampuls on a rack or holding them in the hand, the solution can be easily poured into them to the desired amount, sealed and then sterilized.

The only possible objection to this method may be the fear of contamination of the solution, but this seems to be rather untrue. If the filling of the ampuls as above described, is performed in a room where no current of air is circulating, contamination is almost improbable. In one of the universities, twenty-four hour, gelatin cultures of the air of a room were taken, and it was found to be perfectly free from any bacteria, so that the above method of filling ampuls can be carried on with absolute certainty that the ampuls will be bacteria free.

The commercial filling of ampuls should be carried on in places remote from large cities because there is less danger of contamination by germs.

A kind of multiple burette is used by Paillard-Ducatte of Paris, under the name of "Semplissodosseur." There are other modifications of the burette which are used and employ the same principles. For example, the Pegurier and the Falck stock bottles which involve more or less the same principles of gravity filling and therefore employ and work by the same method as that of the simple burette and therefore require no further explanation.

In the same way since about two decades (1896-7) Professor Alexander von Poehl of St. Petersburg filled his spermin ampuls with 1.7 cc. of a solution, which contained physiological salts in the same proportion as those found in the blood.

PRESSURE FILLER.

The hypodermic syringe furnishes a convenient and simple form for filling ampuls. An all-glass syringe should be used for filling ampuls by this method. A syringe of this kind allows perfect asepsis and accurate dosage. All that is necessary to do, is to sterilize the syringe by boiling it in distilled water. All parts of the syringe can be taken apart, so that complete sterilization of the

syringe is possible. The syringe is then filled with the solution and gradually poured into the ampuls, filling them with any quantity of the solution desired. The ampuls are sealed in the bunsen flame and then sterilized.

In the Journal of the American Pharmaceutical Association, May, 1914, Mr. H. A. B. Dunning, of Baltimore, said that a very simple process in use, in his establishment for making camphorated oil ampuls, was to simply fill the ampul by using the hypodermic syringe, seal the ampuls and sterilize them.

The only possible objection to this method may be that the air in the ordinary dispensing room would be contaminated. This can be overcome by the manufacture of an aseptic hood, consisting of an air-tight box provided with a glass window in the top and a glass side through which light may be admitted, the front containing two arm holes through which the hands of the operator may be thrust. A bunsen burner can be also placed in the hood with a suitable outlet for the gases and in this way the process of filling and sealing can be carried on aseptically.

FILLING BY MEANS OF A VACUUM.

The best method for filling ampuls is that in which the use of a vacuum is involved. A rather ingenious method of filling ampuls by vacuum has been tried by Dr. J. Leon Lascoff and found advantageous.

This apparatus has been fully described in a paper on "Camphorated Oils in Ampules," in the Journal A. Ph. A., Vol. 3, 1914, p. 689, in a paper which was presented by the chairman of the section on practical pharmacy and dispensing at the Nashville meeting of the A. Ph. A.

This is a very simple method and can be operated by almost anybody. The principle involved is that by removing the atmospheric pressure of fifteen pounds to the square inch, the liquid will rise in the ampuls to the height of the air pressure plus the pressure exerted by the weight of the solution.

The quantity of liquid that the ampuls contained has been measured and each ampul has been found to contain exactly 2 cc., which in the case of a bichloride of mercury solution, represented seven and a half grains of bichloride of mercury.

Camphorated oil ampuls have been filled in the same manner.

There are many other devices used by different people which work practically under the same principles involved above and therefore need but mentioning of the makes. An apparatus used by Fairchild Bros. & Foster, also the Eury apparatus described by Pegurier and the apparatus described by Spindler in the Pharmazeutische Zeitung for 1908, made by Auer, of Zurich, all work by vacuum and work by principles similar to that described above.

The above described apparatus is probably the most convenient and satisfactory method of filling ampuls, also inexpensive to construct and easy to sterilize and can be used not only on a small scale, but also on a large scale, for by adding more glass containers you can increase the filling so much more. Its use is well within the limits of any enterprising pharmacist.

TO TEST THE SEALING.

In sealing the point of the ampul, it is not always easy to make sure that the sealing is perfect. This can be readily tested by boiling the filled ampuls in a solution of methylene blue, one grain to two ounces of water, and allowing the

ampuls to remain there until the solution cools. In case the tubes are imperfectly sealed, the color will show in the contents of the ampuls, after having cooled in the solution.

STERILIZATION.

The importance of complete sterilization of ampuls and their contents cannot be too strongly accentuated. Its extreme importance can be seen from the coming Ninth Revision of the United States Pharmacopœia and the Fourth Revision of the National Formulary, which contain a chapter on sterilization and from which the following matter has been in part taken. Much care must be exercised at every stage of the operation of making solutions and filling them to insure complete sterility. The utensils, the solvents and the substances used must be sterilized and protected from contamination.

The term "Sterilization," as employed in the practice of medicine and pharmacy means the destruction or removal of bacteria or their spores and other living organisms. This may be accomplished in various ways. depending upon the nature of the object to be sterilized. A sterile condition can be maintained only as long as the substance or object is kept from contact with air or other media which may carry micro-organisms.

These organisms may be pathological. In this case, it would be very harmful if a solution of this nature would be injected into a sick person. It would undoubtedly create a new sickness but a danger of this kind is not very great compared to a second danger, in that the germs which are not pathological at all, are constantly splitting and changing the dissolved organic compounds contained in the solution. In this case, it is very much more important that the ampuls be sterile, more so than the injecting syringe because the contained liquid remains months and years in contact with the ampuls, whereas it only remains a few minutes in contact with the injecting syringe.

GLASS UTENSILS.

These may be sterilized by heating them from 160° to 170° C. for two hours in a hot-air sterilizing oven or in a closed vessel (autoclave) under steam pressure at a temperature of from 115° to 120° C. for fifteen minutes. Heating in a current of steam for thirty minutes, or thoroughly boiling for fifteen minutes in water or an aqueous solution of sodium bicarbonate (1-1000) will kill all non-spore-bearing organisms and some spore-bearing organisms. As the presence of even a minute quantity of alkali is frequently objectionable in glass containers, the process of sterilization should in such instances be preceded by a thorough cleansing of the bottle, ampul or other receptacle with one percent hydrochloric acid, followed by a thorough rinsing with distilled water.

It is also possible to sterilize with an alkali solution but must be followed by a new cleaning with an acid solution.

MEDICINAL SOLUTIONS OF SUBSTANCES NOT READILY DECOMPOSED BY HEAT.

Solutions which are not injured by high temperature should be sterilized in a current of steam or in an oven in a closed apparatus (autoclave) by steam under pressure.

Sterilization in a current of steam should not be concluded in less than thirty minutes and the heat should preferably be continued for one hour. An exposure

of from fifteen to twenty minutes is sufficient if the sterilization is carried out in a pressure apparatus at a temperature of from 115° to 120° C.

MEDICINAL SOLUTIONS OF SUBSTANCES READILY DECOMPOSED BY HEAT.

With substances affected by heat there is danger of decomposition at high temperatures and Tyndallization or intermittent sterilization must be resorted to. In these cases the ampuls should be heated to 60° C. for half an hour at intervals of twenty-four hours for three or four consecutive days.

SUBSTANCES DECOMPOSED BY HEAT.

Hager's Handbuch der Pharmazeutischen Praxis, states that solutions of the following substances are liable to decomposition at the boiling-point of water: Atropine, cocaine, hyoscine, scopolamine, duboisine, physostigmine, atoxyl and ergot solutions. Acid hydrochloride of quinine and urea is also liable to be decomposed.

From the statements of other scientists, chemically pure products of these alkaloids and other compounds can stand a very much higher temperature than 100° C. without any decomposition. It is not the object of my thesis to decide these contradictory statements.

It is not to be wondered that some of these questions relative to ampuls are undecided, as ampuls have only been lately introduced and therefore more special research work is needed.

ADVANTAGES OF AMPULS.

The fluid preparations of ergot, digitalis and strophanthus deteriorate more or less rapidly under ordinary conditions. The principal causes of such deterioration are oxygen of the air and heat, therefore recently manufacturers have taken advantage of ampuls and are putting up preparations of the above substances in ampul form. It is a known fact that fluidextract of ergot retains its activity for a much longer period of time when kept in well-filled and tightly-stoppered containers, which precautions can be had through the use of ampuls.

Ampuls are always ready for immediate use. It is no longer necessary, as in making up solutions from powder or tablet, to wait until the water can be sterilized and cooled. The solution is accurately adjusted to contain a specific amount of medicament in each cubic centimeter, thus insuring accuracy of dose.

The solution is ascepticised by heat or by filtration through porcelain, as its nature demands. The drug is treated with the most suitable solvent, whether that be olive oil, distilled water, or physiological salt solution.

Permanence is attained by means of the hermetically sealed container which protects the contents from bacterial contamination and from oxidation, while actinic effect of light is prevented by the use of amber ampuls and by enclosing the glass ampuls in an impervious cardboard carton.

In hospitals, the preparation and preservation of solutions is a matter of little difficulty but to the busy general practitioner it is a source of annoyance and inconvenience and to say the least, is in many cases decidedly unsatisfactory; hence, the advantage of using ampuls.

Especially during war time, a great deal of ready medicine must be at hand, both on the battlefield and in the hospitals. It is true that many tablets and

powders are always ready at hand, but how much more convenient and time-saving would the ready ampul be.

It is absolutely necessary that only distilled water be used, as ordinary tap water, on account of the presence of bacteria and foreign matter, is objectionable. Few physicians have distilled water constantly on hand in their offices, and especially in time of war, the possibility of securing distilled water in a non-contaminated room, on the battlefield, is hopeless and to procure the necessary amount from the usual sources of supply, at times of peace and more so during times of war, is time-consuming and otherwise inconvenient, hence the advantage of using prepared ampuls.

It is manifestly all important that solutions for hypodermic injection should be sterile. It is likewise evident that physicians are very frequently unable to prepare sterile solutions extemporaneously, especially on the battlefield during times of war and therefore by using ampuls, all of these difficulties can be overcome.

THE POSSIBILITIES INHERENT IN A COLLEGE OF PHARMACY FOR RENDERING THE MAXIMUM OF EFFICIENT SERVICE TO PHARMACY.*

FREDERICK J. WULLING.

I am to speak upon the future possibilities inherent in the St. Louis College of Pharmacy. The possibilities of this college are the same in kind, as those of any other. The fundamental purpose of any high-grade college is, or should be, to render the maximum of efficient service to the calling and through the latter to the public. To render the most efficient services a college must meet many requirements and must conform to some quite definite standards. Some thoughts that have come to my mind in the matter I have formulated into an outline which I submit herewith and which I will use as the basis of some remarks:

Composition of the college.—1. Governing body, 2. faculty, 3. quarters, 4. equipment, 5. students, 6. alumni. All of these are organized to render the maximum of efficient service to (a) the student body, (b) the profession, and through these to (c) the public.

Under the heading of governing body comes the consideration of business administration, which includes executive faculty officers; budget; clerical assistance; card indices; statistics; co-operation with faculty; appointments; salaries and salary scale; faculty promotion; research; fellowships; scholarships; publications; future development and extension work.

Under the heading of faculty comes the consideration of organization, which includes executive faculty; executive officers; classification of teachers into dean, professors, assistant professors, instructors and assistants; conferences; aca-

* An address delivered at the fiftieth anniversary of the St. Louis College of Pharmacy.