

# SECTION ON COMMERCIAL INTERESTS, AMERICAN PHARMACEUTICAL ASSOCIATION

## HISTORY OF SUBSTITUTES AND SUBSTITUTION.\*

BY OTTO RAUBENHEIMER.

Everything has its history, even substitution! Most writers trace the origin to Claudius Galenus of Pergamos and later of Rome. However, Dr. Felix von Oefele, the celebrated Assyriologist and Egyptologist, now in New York City, and also a member of the A. Ph. A., has made further researches, which are quoted by Schelenz in *Geschichte der Pharmazie* and by Tschirch in his *Handbook der Pharmakognosie*. Oefele was also kind enough to give me the additional information that records of substitutes and substitution existed in old Assyria, namely, in the library of King Sardanapalus, who reigned from 668 to 626 B. C. Ashurbanipal, which is the Assyrian name, the warrior King, destroyed innumerable cities of high civilization in Babylonia, Elam and other countries. He tried to make Nineveh the center of the civilized world, especially by one of his aims, namely, the creation of a large library of copies of older texts, collected in the destroyed cities. The principal medical and pharmaceutical texts of Sardanapalus' library were copies from the old city Nippur, and as ruins Niffer, which was excavated by the University of Pennsylvania. About twenty thousand of these clay tablets from the library of Nineveh are preserved in the British Museum, and more than one thousand contain medical and pharmaceutical matter. The Niffer tablets now at Philadelphia show that the Assyrian King had not left many of the original scientific texts at Nippur.

Dr. Oefele discovered that some tablets contain a special form of tabulation, namely, in two columns. **The drugs mentioned in the left column can be substituted by drugs in the right column.** The drugs are not mentioned by name, they are stated as parts of the body of a god or his devoted animal. A group of alternating substitutes could have the same name of the god or animal.

Dr. Felix von Oefele deserves credit for the correct translation and explanation of the old medical papyri, having first brought this subject before the Section of History of Medicine at the meeting of the German Naturalists at Duesseldorf in 1898. Inasmuch as several plants of almost identical properties are dedicated and named after the same deity, a correct interpretation is not an easy task. For instance, *Succus Anethi recenti expressus* was named *Blood of Ibis* and *Semina Anethi* were called *Hairs of Kynocephalus*. Ibis and Kynocephalus were both animals devoted to Thoth, *i. e.*, the Egyptian Hermes. Artemesia was called *Heart of Bubastis* and *Blood of Hephaestus*.

Such synonyms were undoubtedly originated by the priest-physicians in Egypt to conceal the identity of the drug from the laity. Squill grew in the vicinity of Pelusium, where dropsy was endemic. The evil god Typhon was said to live near by in a swamp, consequently, squill received the synonym *Eye of Typhon*.

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\* This paper, the one following on "*Ersatz-Praeparate*," by H. Engelhardt, and "*Quid pro quo* in U. S. P. IX," by Otto Raubenheimer, constituted part of a Symposium on Substitution, prepared for the Section on Commercial Interests, A. Ph. A., Atlantic City meeting, 1916.

That even a synonym-lexicon existed as early as 200 B. C. is proven by the publication of a Greek papyrus by Leemann and Dieterich in 1888. The *Papyrus Brugsh* dating to 1500 B. C. also contains a small synonym-lexicon.

Dioscorides (abt. 50 A. D.) in his *materia medica* also gives a large number of synonyms.

In those early days substitution was frequently demanded by the patients themselves, as can be seen from the following incident told in Friedlaender's *Roman Life and Manners*:

"As the opinion was that the dearest medicines were the most efficacious, and the rich, therefore, would have nothing cheap, the apothecary business was extremely profitable to the practitioner. One rich man, whose slave Galen had cured of a dangerous tumor, asked for the recipe, saw that its ingredients were cheap, and demanded something not fit for beggars. Galen then taught him a more expensive recipe."

Another example of substitution is the following: Precious stones were largely used in medicine in ancient times. For the plutocrats the most expensive were used, as, for instance, the emerald as a green stone. For the middle class a less precious stone was taken, probably some form of chrysoprase, and the poor received ordinary malachite, or the still cheaper green Egyptian porcelain. Here is still another example: Sapphire was precious and expensive, *Lapis Lazuli* was less expensive and Babylonian Blue Glass was cheap.

These different qualities in medicine according to circumstances of three milleniums ago have survived up to now in the expressions *optima*, the best; *vera*, the true; *communis*, the ordinary; and *canina*, the bad (good for the dogs), adulterated and useless.

Claudius Galenos of Pergamos, Asia Minor (130-200), the celebrated physician at Rome, prepared a list of *Anteballomena* or substitute drugs. He was called to a patient on the death-bed and wanted to administer *Semen Acanthii*. Unable to get same in a hurry, he took in place *Semen Lychnidis*. Thereupon, his colleagues in Rome asked him to prepare a list of substitute drugs, which is one of the oldest and most complete records of substitution in the Greek language.

A later legend tells that Galenos found older lists of substitutes and copied same. The later physicians believed these lists to be compiled by Galenos.

The works of Galen remained the undisputed medical authority for about 1400 years until a young Flemish physician, Andreas Vesalius (1514-1564), discovered grave mistakes in Galen's anatomy and until Paracelsus (1493-1541) became the iconoclast or image breaker of the old medical school.

The *Antidotarium* of Nicolas Praepositus, the director of the celebrated medical school at Salerno about 1100, contained a *Tractus quid pro quo*, consisting of a list of substitutes, arranged alphabetically.

Johannes Actuarius, court physician at Constantinople at the end of the 13th century, wrote a *Quid pro quo* as an appendix to his works.

The *Ricettario Fiorentino* (1498), one of the early pharmacopoeias, contained a *Tractus quid pro quo*.

The first official pharmacopoeia in Germany, namely the *Dispensatorium of Valerius Cordus*, published in Nuremberg in 1546, contains an appendix, *De Succedaneis quid pro quo*, in which the following are some of the substitutes:

|               |                              |
|---------------|------------------------------|
| Bitter Almond | replaced by Wormwood         |
| Colocynth     | replaced by Ricinus (seed)   |
| Ginger        | replaced by Pyrethrum (root) |
| Zedoary       | replaced by Aristolochia     |

These examples no doubt prove that the old books on medicine and the dispensaries contained regular lists of substitutes. Why? The answer is threefold.

- (1) As a matter of convenience for physician, pharmacist and patient.
- (2) As a matter of necessity.
- (3) Because frequently certain drugs were unobtainable, as commerce to the Orient, which was the source of most drugs, became interrupted. Do not the very same conditions exist to-day?

So much for the origin of substitutes and substitution. Now as to the step taken against substitution. The Edict of Emperor Frederic II in 1227, which can be justly considered the first pure food and drug law, and which separated pharmacy and medicine, also contains a provision that the *stationarii* (because they were stationed in monasteries) and the *confectionarii* (the forerunners of our confectioners) must prepare the medicines according to the prescription of formula and must not cheat by the use of *Quid pro quo*. This law forbade all substitution, under penalty of confiscation of all goods, if done without consent of the prescribing physician.

Saladin of Ascolo or Aesculanus, the celebrated *Artium et Medicinæ Doctor* in Salerno, states in the 4th part of his book, the first modern pharmacy book, *Compendium Armamentarium*, that the apothecary has no right to take any *Quid pro quo* without the consent of the physician. The pharmacist is also ordered to take the very best variety or species of a drug, when same is merely ordered by its generic name!

In the first half of the 17th century, Dr. Guy Patin, dean of the Medical Faculty at Paris, attacked the pharmacists in a sarcastic manner and accused them of substitution.

Such complaints were repeated from time to time and were the cause that pharmacists received the name *Quidproqueur*. This cry of substitution has been kept up ever since, more or less unfounded!

Let us consider, as a matter of history, the advantages of substitutes, advantages which have made it worth while to write the history of substitution.

#### USE OF INDIGENOUS DRUGS.

Strange as it may seem, there are 6 **different** nations in 6 **different** parts of the world who use 6 **different** plants or drugs as food and drink. However, these 6 drugs belong to one group, the purin group, and they contain the same active constituents, namely, Caffeine. I refer to the coffee of the Arab, the tea of the Chinese, the cola of the African, the cacao of the Central American, the guarana of the Brazilian and the *maté* of the South American. Unknown to each other, these different nations used these different drugs for the same purpose, namely, as a stimulant!

The Chinese do not employ any other drugs but those indigenous to China. It has been the desire of all nations to use domestic drugs as their *materia medica*.

In fact Paracelsus even went so far as to claim that it was impossible to cure a disease in Germany with drugs grown on the Nile!

Much has been written urging each country to make use of the indigenous drugs and to replace foreign drugs with domestic ones. One achievement along these lines is the cultivation of drugs, that is, the **substitution of home-grown drugs for imported ones**. As examples we have American Cannabis in place of Indian Cannabis, American Belladonna in place of the European, American Peppermint in place of the English-grown.

#### SYNTHETIC SUBSTITUTES.

The advances made in chemistry have been wonderful! Ever since Friedrich Woehler synthetized urea by heating together ammonium chloride and silver cyanate, organic chemistry has produced many synthetic or artificial products, for instance, salicylic and benzoic acid, methyl salicylate, artificial oil of mustard and oil of rose, camphor, indigo and rubber.

Many alkaloids are now manufactured synthetically, as codeine, piperine, cocaine, caffeine and adrenaline. These synthetic products are identical with the natural ones, excepting that on account of their high purity, they do not act upon polarized light.

#### NEW DISCOVERIES.

In looking for substitutes chemistry has been enriched with many discoveries. One of the oldest records along this line is the discovery of sugar in the beet and the resulting beet sugar industry in 1747 by the German apothecary Margraff, in looking for a substitute for the expensive cane sugar. Another example is the discovery of the beautiful aniline dyes, which have almost replaced the old vegetable dyestuffs.

#### CHEMICAL SUBSTITUTION.

This theory was introduced by the French chemist Dumas and means that the hydrogen atoms in organic substances can be removed one by one from their molecules, other atoms being substituted for them. Although this is a different kind of a substitution, it belongs to this subject just the same.

#### AMERICAN MINERAL WATERS.

Owing to the war it is extremely difficult to obtain foreign mineral waters or to visit the spas themselves. Prof. Felix von Oefele deserves credit for making a very valuable compilation of the principal foreign mineral springs together with their equivalent in this country. Nothing but a substitution and a valuable one at that! This paper was published in the *Bulletin of the College of Jersey City*, Vol. II, No. 3, January 15, 1915, and *JOUR. A. PH. A.*, May 1915, p. 617. It was also highly commented upon by James H. Collins in "Raising Our War Babies," in the *Saturday Evening Post* of April 29, 1916, in which he states: "Altogether we have found good substitutes for about 100 of the foreign *inbads* and *badofs*."

#### SODIUM SALTS IN PLACE OF POTASSIUM SALTS.

Owing to the great scarcity of potassium salts and the consequent enormous increase in price, the respective sodium salts have been recommended as substitutes. Besides their lower price, sodium salts have two further advantages over potassium salts, namely, a smaller molecular weight and greater solubility. One

large chemical manufacturer in the United States has made an active propaganda among physicians and pharmacists in order to give sodium salts the preference.

#### SUBSTITUTES IN PHARMACOPOEIAS.

That pharmacopoeias do not hesitate to use and to authorize substitutes can be seen from the following:

*Deutsches Arzneibuch 5, Ausgabe, 1910*, states in spaced type, very prominently: "Tinctura Ipecacuanhae shall be dispensed when Vinum Ipecacuanhae is ordered." "Magnesium Sulfuricum, Natrium Carbonicum and Natrium Sulfuricum: the dry or exsiccated salts shall be used instead of the crystalline in mixtures of powders."

In another paper I present the *Quid pro quo* in U. S. P. IX.

The most extended form of substitution exists in the British Empire. The principal object of the *Indian and Colonial Addendum* is the substitution of drugs indigenous in that particular part of the British Empire. The following are some of the substitutes: Arnica flowers for the root in the North American colonies; species of *Datura* for *Belladonna* leaves in East and West Indies. *Embelia* fruit for *Kousso* and Male Fern in East India. Cottonroot bark for Ergot in East and West Indies and North American colonies.

The new British Pharmacopoeia, 1914, which is said to be adapted to all parts of the British Dominions, also contains a great number of notes, in small type, at the end of the monographs, sanctioning substitution of a similar drug, for instance, under *Kino* and under *Butea Gummi*: "In India and the Eastern Divisions of the Empire, *Butea Gum* may be employed in making the official preparations for which *Kino* is directed to be used." Under *Gummi Indicum*, but not under *Acaciae Gummi*, this statement is made: "In India, etc., Indian Gum may be employed in making the official preparations for which Gum *Acacia* is directed to be used, one part of the former being taken for every two parts ordered of the latter."

In Appendix XII of the new B. P. on Alternative Preparations sanctioned for use in Tropical, Subtropical, and other Parts of the British Empire, I find the following:

"*Oleum Olivae*.—In India, and in the Eastern, African, Australasian and North American Divisions of the Empire, *Arachis Oil* or *Sesame Oil*, but no other oil or fat, may be employed in making the official Liniments, Plasters, Ointments and Soaps for which *Olive Oil* is directed to be used."

**If this is not a dvocating, in fact, soliciting substitution, then what is it?**

#### SUBSTITUTES FOR DRUGS.

Owing to the war and the resulting scarcity of imported drugs, the pharmaceutical and medical journals of Germany and Austria have published lists of substitutes for vegetable, animal and mineral drugs. Truly, not a great deal of difference from the *Quid pro quo* lists of 2 millenniums ago!

Dr. H. Engelhardt, of Baltimore, was good enough to abstract formulas for *Ersatz-Praeparate* of Oils, Fats, Ointment Bases, Lanolin, Vaseline, Glycerin and Soaps.

#### SUBSTITUTE FORMULAS FOR SPECIALTIES.

My paper on this subject, published in *JOUR. A. PH. A.*, August 1915, p. 952,

describes the two principal booklets, namely, the *Formular des Luxemburger Apotheker Verein* and the *Sammlung von Vorschriften fuer Zubereitungen zum Ersatz von Spezialitaeten des Feindlichen Auslandes* (Collection of Formulas for Substitute Preparations of Specialties from Belligerent Countries).

This shows the trend of substitution in Germany. According to the Kaiser's proclamation on July 31, 1915, pharmacists and manufacturers are asked to replace foreign specialties by those **made in Germany**. After May 1, 1915, no more foreign names or labels can be used and according to *Pharm. Ztg.*, Aug. 7, 1915, p. 511, a druggist was convicted to 2 days in jail for using labels *Eau de Javelle* and *Eau de Botot*.

Verily we live in an age of substitution!

However, let us get away from that ill-smelling word Substitution, and adopt one which sounds much better, namely, **Parallel Drugs and Chemicals**.

#### PARALLEL DRUGS.

This term has been first introduced in 1897 by Prof. Carl Hartwich, of the University of Zurich, in his book, *Die Neuen Arzneidrogen*. Prof. Alexander Tschirch, of the University of Berne, the world's greatest authority on pharmacognosy, has helped to popularize this word.

The writer has done likewise and has published an editorial in the *Bulletin of the College of Jersey City*, Vol. III, No. 3, Feb. 1, 1916, which has also been reprinted in the monthly *Drug Bulletin* of the Department of Health, City of New York, for July, 1916.

Inasmuch as this editorial also contains an appeal to pharmacists, I shall use it as a finish in my paper on *History of Substitutes and Substitution*.

The substitution of one drug for another has been practiced from the earliest times. Was it not Claudius Galenus (130-200 A. D.), the great Roman physician-pharmacist, who was about the very first to prepare a lengthy list of drugs, *Quid pro quo*, a list which remained in use until about the 16th century?

These substitute drugs, which in Latin were called *Succedanea* or *Aniemballo-mena*, were considered of such great importance that they were included in the old pharmacopoeias. Of late years the substitution of a drug by a similar drug, especially on prescriptions, has even been forbidden by law. This is justly right, because the physician "wants what he wants when he wants it."

However, at the present time, owing to the war, the supply of a great many drugs and chemicals from Germany—and the Fatherland seems to be the only producer of same, especially the coal-tar products—has been entirely cut off by Great Britain, the so-called *ruler of the seas*. The great scarcity of some drugs and chemicals and the high price of others suggest that substitution will again come to life. Not an underhanded, illegitimate substitution, without the knowledge of physician or patient, but a perfectly legitimate substitution. In order to get rid of that ill-smelling word **Substitution**, the editor proposes the term **Parallel Drugs and Chemicals** in place of **Substitute Drugs**.

Now is the right time for the pharmacist to use his knowledge of pharmacy, chemistry and materia medica and to inform the physician of **Parallel Drugs and Chemicals**. Now the pharmacist has a golden opportunity to prove to the medical profession that "Pharmacy is the handmaiden to medicine."

Will he do it?