

some or impossible for the manufacturer to produce without adding unnecessary and excessive cost to the consumer."

With the foregoing meagre generalities the profession is left to draw its own conclusions—some of which will doubtless be correct; but all of which must be uncertain. But the scientific mind is not and never can be content with mere conclusions. Its demands are ever for a knowledge of the premises upon which the conclusions were based—so that it can check the conclusions and accept them upon their merits or revise them if they be found faulty.

A REVIEW OF THE CHEMISTRY OF DIGITALIS.*

C. H. KIMBERLY, M. SC., PH. D., MEDICO-CHIRURGICAL COLLEGE, PHILADELPHIA.

Digitalis plays such an important part in our present day medicine that its chemistry should be well worked out. If one should read but one report, it would so appear, but the deeper one probes into the results of chemical investigation, the more confused he becomes and finally finds himself unable to decide positively of what it really does consist.

Tracing the steps of its investigation, we find in 1820 it was examined by Pancquay, in 1824 by Lancelot and in 1834 by Leroyer; also about this time it was studied by Homolle and Quevenne. Both Leroyer and Lancelot described a crystalline principle, while Homolle and Quevenne claimed its active principle to be amorphous. In 1868, Nativelle isolated a crystalline principle, but he later thought this to be a compound body. In 1871 Schmeideberg^a and Killiani independently took up the work and each isolated a crystalline principle which they called *digitoxin* and it appeared that this was the same principle described by Nativelle. For some time this substance commonly known as *digitalin* was the only principle known and a number of substances classed as both scientific and commercial were exploited under that name.

It soon became evident that these products were mixtures, also that digitalin was not the only active constituent, and further effort by Schmeideberg produced the isolation of four glucosids, namely *digitonin*, *digitoxin*, *digitalin* and *digitalein*, and he proved also that the digitalin of commerce consisted of various mixtures of these glucosids. He found it difficult to obtain these glucosids in a pure state on account of their easy decomposition. In the years between 1892 and 1899 Killiani confirmed this contention of Schmeideberg, and increased our knowledge of digitalis by information relative to the decomposition products. Work along similar lines during the same and following years has been done by Keller, Cloetta, Boehm, Bargar and Shaw, Brissemoret and Joanne and others though the principal authorities still are Schmeideberg, Killiani and Cloetta. At the present time on account of the complexity of digitalis and the ease with which its constituents decompose it is difficult to isolate them in a pure state, and we are compelled to say "we believe" rather than "we know."

According to Schmeideberg and Killiani, we have the following constituents:

* Read before the Scientific Section of the Philadelphia Branch.

digitoxin, digitalin, digitalein, digitophyllin, digitonin, digitin, digitoflavin fixed oil, volatile oil, starch, gum, sugar, inosit, pectin, red and yellow coloring matter, digitalosmin (stearopten), antirrhinic acid, digitalic acid, and in fresh leaves an oxydase,^b a ferment, as well as decomposition products, such as digitoxase, etc.

Digitoxin $C_{34}H_{54}O_{11}$ (Killiani) is present in the largest quantity, the yield from the leaves varying from 0.22 to 0.4%, the average according to Ceasar and Loretz in the analysis of forty-seven samples being 0.25% and according to Kain 0.30%. The yield from the seeds is much less and Killiani questions if it is present at all. Schmeideberg is doubtful as to the character of this product, but Killiani claims that it is a glucosid. It is insoluble in water, but somewhat soluble in the presence of other glucosids particularly digitonin. It is readily soluble in alcohol and chloroform, but is insoluble in ether, and Keller and Panchaud claim it is precipitated from a chloroform solution by means of ether. It readily splits up into *digitoxigenin*, which is soluble in water, *digitoxan*, a sugary body, and glucosid called by Schmeideberg, *toxiresin*. This hydrolysis takes place best in alcoholic hydrochloric acid solution. Digitoxin (crystal) is claimed by Petit and Polonowski to be identical with the French commercial product, *digitaline* of Nativelle. Digitoxin (crystal Merck) is claimed also to be the same qualitatively as *digitaline*. Digitoxin amorphous soluble, is claimed by Cloetta as an isomer of digitoxin crystal, but it is found in small amounts only in the leaves and is thought to be *digalin* or a mixture, but certain claims of Killiani as to its being a mixture, largely digitalein has not been proven by experimentation.

It appears that digitoxin is the most abundant and important constituent and is found in both the leaves and the seeds, but only in small quantity in the seeds.

The commercial articles are generally not of great reliability on account of their being mixtures and hence not capable of standardization.

Digitonin was first obtained in a crystalline condition by Killiani, by extracting the commercial German digitalin, of which it is the largest ingredient, with a mixture of absolute alcohol and chloroform and then precipitating by the addition of ether. It has a formula $C_{64}H_{72}O_{28}$ (Killiani). It is classed as a saponin, holds digitoxin in solution and breaks down into digitogenin, dextrose and galactose (Cloetta). Killiani claims that the decomposition products are sapogenin (similar to digitogenin) and a mixture of glucose and galactose. Digitonin crystalline (Killiani) and digitonin amorphous (Schmeideberg) are entirely different substances, but Cloetta ^d after extensive study thinks this difference is largely due to the impurity of the product of Killiani.

Cloetta, Kellar and Killiani all found digitonin in both leaves and seeds. Killiani claims that the seeds contain a considerable amount, but the leaves very little. Digitonin is said to be a saponin, and as such it assists in holding other constituents in solution.

Digitalin $C_5H_8O_2$ ^{d^e} as isolated by Homolle was later found to be a mixture of digitalin, digitoxin and digitogenin and is non-crystalline. The so-called digitalin is a mixture of digitalein and digitonin, digitalin and digitoxin. It is a commercial preparation usually amorphous in character and is soluble in

water and alcohol. Digitalin Nativelle is a crystalline product and consists largely of *paradigitogenin*.

Digitalinum Verum is the main constituent of the seed, and if present in the leaves is in very small amounts. It has a formula $C_{35}H_{56}O_{14}$ (Killiani) and is thought to be present in 3 to 4% in the plant. It decomposes so readily into digitalogenin and digitalose that its percentage is hard to determine. It is usually amorphous in character. It is insoluble in chloroform and water but soluble in alcohol. Schmeideberg says it is identical with the digitalin glucosid and is essentially the same as the others mentioned as commercial products.

Digitalein (Schmeideberg) is a mixture of digitoxin, digitonin and digitalein and is present in considerable quantity in commercial digitalins. It is distinguished from digitalinum verum by its solubility, since it is soluble in water and alcohol. It is described as a yellow amorphous mass although it is also claimed that there are two kinds, namely, the amorphous and the crystalline. It has properties similar to a saponin, assists in the solution of other principles and in a water solution it foams and rapidly becomes sour. It is, however, not well characterized.

The other principles of digitalis are of less importance, and to some extent also less understood. The opinions are held, however, that digitophyllin has a formula of $C_{32}H_{52}O_{10}$, is a modified digitoxin and is found only in the leaves.

Digitin is considered by many to be the same as digitonin.

Digitoflavin b $C_5H_{10}O_6 + H_2O$ is not well known, but is thought to play a part in the coloring of the plant.

The commercial products are quite well known and need no special consideration here. It need only be said that while many claims are made for each, that they are not well characterized substances, cannot be well standardized and hence should be handled with much caution.

The methods of assay are mainly based on the content of digitoxin, but since the other principles so largely modify the action of digitalis, this would seem to be unreliable.

The method most used is that of Keller^f which is based entirely on this principle and is dependent upon the solubility of this principle in 70% alcohol. The sample is extracted with alcohol, the alcohol is evaporated, the residue is diluted with water, this solution is precipitated with lead subacetate, the excess of lead is removed by sodium sulphate and the filtrate is made alkaline with ammonia. This is extracted with chloroform, purified with petroleic ether and later with alcohol and ether.

Fromme^g modifies this method slightly in the original extraction and Staeder^g proposes a different method which is found in *Phar. Zeit*, 1901, vol. 45. Chemical assays, however, seem to yield poor results, and when checked by physiologic tests the two methods do not give comparative results. Zeigenbein,^h Bühner,^e Bargar and Shaw,ⁱ Reed and Vanderkleed,^j and others have performed these tests, and while the latter obtained results more nearly alike, yet they all seem to prove the inefficiency of our present assay methods in determining accurately by chemical assay the active constituents. Moreover, Bargar and Shawⁱ made up solutions with known amounts of digitoxin and state that they could isolate only 25% of that known to be present. Other authors have obtained

better results but apparently far short of the true amount. It would seem therefore that a large amount of chemical investigation is a necessity before digitalis can be properly standardized by chemical analysis alone, and a vast field of chemical research lies before us.

REFERENCES.

- a. Lehrbuch d. intox. Kobert. 2d ed., vol. 2.
- b. Ber. die deut. chem. gesell. 1905.
- c. Jour. Med. Assoc., vol. 49, 1908.
- d. Arch. f. exp. path a pharm., vol. 45-1901.
- e. Corresp. f. schweiz. arzte vol. 30, 1900.
- f. Centralblatt. vol. 68, 1897.
- g. Ber. d. deut. phar. gesell. vol. 7, 1897.
- h. Arch. d. phar. 1902.
- i. Yearbook of Phar. 1904.
- j. Am. Jour. Phar. vol. 80, 1908.
- k. Russ Phar. Zeitsch. vol. 24.

THE MANUFACTURE OF COAL TAR AND COAL TAR PRODUCTS.*

GEORGE MCDERMAND.

About ten years ago the Denver Gas and Electric Light Company saw the possibilities of manufacturing and selling coal tar products in Colorado and the Western States. A plant was erected and roofing and paving materials manufactured. In a few years the sales were so great, with the demand for the products steadily increasing, it became imperative that a larger plant be constructed. The result was that a modern up-to-date tar plant with a large capacity and equipped to go more thoroughly into the manufacture of these compounds was erected. The amount of tar worked up into salable material by this plant is 100,000 gallons per month.

Coal tar is obtained during the process of gas manufacture. It is collected from the hydraulic mains and gas condensers, and after passing through a separator to relieve it of ammonia liquor, is stored in large wells until used in the manufacture of tar products.

Coal tar mixed with tar oils is extensively used as a paint for iron work and is used on the bottom of ships to keep them free from barnacles. It is also used for painting roofs, wooden buildings, fence posts, etc. Tar paint is an excellent wood preservative, as it contains a large amount of creosote. Paints that are composed of coal tar are very durable owing to the fact that tar is non-corrosive and free from oxidation.

Coal tar without water content is used in manufacturing tarred felt. Modern saturating machines convert the dry felt into uniform rolls of tarred felt. The roll of dry felt is placed on a spindle at the end of the saturating machine; it is run down into a saturating tank about five feet and is kept in the tar by an idler; after coming from the tar it is run between two rolls, where the surplus tar is pressed out, from which it is wound on a spindle until the roll becomes approximately fifty pounds. It is then taken off and seasoned in a warehouse, which takes about a week, before being wrapped and labeled.

* Read before the Denver Branch.