action to all stable indicators within an inch or two of the pylorus.

The older view that an acid reaction due to hydrochloric acid persists for some distance down the small intestine, and that the acid is only gradually neutralized, is, according to the experience of the writer, erroneous and founded on a misconception—viz., that a considerable amount of chyme is expelled at once from the stomach and is gradually mixed with the alkaline secretions as these are secreted, so that in the end the hydrochloric acid is neutralized. As a matter of fact, the amount discharged at any one opening of the pylorus is small, and the mass is shot out, not into an empty duodenum, but into one charged already with alkaline secretion. In a large number of experiments in which free hydrochloric or strong organic acids such as acetic or lactic were tested for by methyl orange, I have scarcely ever obtained an acid reaction, even within two inches of the pylorus, either in carnivora or in herbivora.

It is interesting to observe the economy of the digestive enzymes of the pancreatic secretion which is attained by such an arrangement of previous secretion into the duodenum of alkaline fluids and the discharge of the acid gastric chyme into a quantity of such secretion. On the old view, since all three pancreatic enzymes are extremely susceptible to mere traces of free hydrochloric acid and are almost instantly destroyed thereby, all the pancreatic juice secreted for the considerable period of time which elapses until the hydrochloric acid has been neutralized would be destroyed. In fact, nearly all the pancreatic activity would be thus removed, for this secretion is poured only into the duodenum, and according to the older views, the acidity persists beyond this portion of the intestine. On the view that the chyme is discharged into an alkaline bath and almost instantly neutralized, practically no such destruction would occur.

According to other authors, who admit that the hydrochloric acid is rapidly neutralized, there is, nevertheless, no alkaline reaction in the small intestine; but, on the other hand, there is a markedly acid reaction due chiefly to acetic acid set free by the energetic action of bacteria upon carbohydrates. This acidity is further said to increase in degree as the intestine is descended even until the ileo-cæcal valve is reached. This view is supported chiefly by a few observations upon clinical cases of fistulæ near the ileo-cæcal valve.

In a large number of experiments upon various classes of animals, I have never found an acid reaction due to any stronger acids than those of the fats of the foods. After a fatty meal, and in the carnivora only, a faintly acid reaction to litmus is obtained; this is, however, due to the weak organic acids set free from the fats by the hydrolytic action of the steapsin, as is shown by the fact that no acid reaction, but instead a strongly alkaline one, is obtained with methyl orange. This acid reaction is too weak to effect the activity of any of the intestinal enzymes, and usually persists for from one-third to one-half the length of the intestine. An acid reaction due to acetic and lactic acids was obtained in one case only, but here the small intestine was also distended with gas, and digestion was obviously not proceeding in a normal fashion. From these experiments it is obvious that in animals of widely different species, and therefore most probably in man also, there is no appreciable destruction or digestion of carbohydrates in the small intestine by the agency of bacteria. Since in a mixed food carbohydrates are attacked before proteids, it is probable that bacterial action upon the mixed food in the intestine is inconsiderable in amount. The degree of alkalinity varies with the food, being greatest on carbohydrates and least on fatty food.

The chief digestive secretions which affect the food in the intestine are the pancreatic juice and the bile, the succus entericus possessing, so far as we know, but a subordinate value as an aid to digestion.

The pancreatic juice contains three important enzymes, each of which has a digestive action upon a different one of the three great classes of food-stuffs; as a result, all the important elements of the food are attacked in the small intestine by the pancreatic juice. Thus, carbohydrates are subjected to the action of the diastatic enzyme, amylopsin; fats are hydrolyzed by the steatolytic enzyme, steapsin; while proteids are peptonized by the proteolytic enzyme, trypsin.

The action of amylopsin resembles in every respect that already described in the case of ptyalin. So close is the resemblance that certain writers state that the two ferments are identical; of this, however, there is no experimental evidence, since neither body has been isolated. Pancreatic juice acts more energetically than saliva upon starches, but this may merely mean a difference of concentration.

Pancreatic juice contains, so far as is at present known, the only enzyme possessing a specific chemical action upon the neutral fats. This action consists in decomposing the fats into free fatty acids and glycerin. Until quite recently it was held that only a small percentage of fat underwent this change, and that the fatty acids so set free combined with the alkali of the intestinal contents to form soaps. In the process of combination it was supposed that the soaps converted the remaining larger portion of undecomposed fat into a fine emulsion which was then absorbed in this chemically unaltered form by the columnar cells.

Recent experimental observations have tended to invalidate this emulsion theory of absorption, and it is now held by many that all the fat of the food is absorbed in soluble form. The chief facts in favor of this view may be summarized as follows:

1. The rapidity of action of steapsin is such as to admit of the saponification of all the fat of a full fatty meal within the ordinary period of digestion.

2. It has never been shown by histological examination that fat particles pass into the columnar cell; on the contrary, the broad striated border of the cell is invariably free from fat granules.

3. Examination of the columnar cells at varying periods after a fatty meal shows that the fat globules seen in these cells continuously grow larger as the period of absorption increases, indicating that the globules are deposited from solution.

4. Although fatty acids are insoluble in water they are fairly easily soluble in bile solutions and exist in solution in the intestinal contents of some classes of animals during fat digestion. The solubility of the different soaps is also greatly increased by the presence of bile in the intestinal contents, and soaps are also found in the intestinal contents during fat digestion.

It is probable from these various observations that the entire fat of the food is hydrolyzed in the intestine to fatty acids and glycerin, that the fatty acids are entirely or in part neutralized to soaps of the alkaline metals by the alkali of the intestinal contents, and that these soaps, or the mixture of soaps and free fatty acids, are absorbed in solution by the columnar cells.

In the columnar cells the constituents of the fats are recombined to form neutral fats, and here it is interesting to note that the columnar cells appear to be capable of furnishing glycerin for the synthesis to neutral fat, for even when free fatty acids are fed, only neutral fats are to be found thereafter in the thoracic duct.

It has been stated above that the action of pepsin upon proteid never amounts to complete peptonization; in addition to this a considerable amount of proteid matter passes through the pylorus which has not been chemically altered at all by the gastric juice. An examination of the contents of the upper part of the small intestine, after a meal containing flesh, usually demonstrates undigested fragments and often pieces of considerable size floating in the thin fluid contents of the intestine. Such macroscopic fragments become less frequent and smaller as the intestine is descended, evidently because of advancing solution, while at the same time the fluid portion becomes thicker, so giving rise to a more homogeneous mass of ever-increasing thickness as the ileo-cæcal valve is approached. The action of trypsin upon proteids is both more complete and more rapid than that of pepsin. The preliminary stages are rushed through more rapidly. The first stage, as mentioned above, is that of alkali albumin, but this substance is rapidly converted into deutero-albumose, this in turn into peptone, and the peptone in great part into amido-acids and organic nitrogenous bases. It is doubtful whether any primary albumoses are formed in the course of tryptic digestion; if they are, the stage is an exceedingly unstable one and they are quickly changed into deutero-albumoses. The deutero-albumoses are easily demonstrated in the earlier stages of tryptic digestion, but are converted later into peptone. The conversion of peptone into simpler bodies proceeds more slowly, and only about half the peptone gets so completely decomposed as not to give most of the reactions of the proteids. The more stable portion is usually termed *antipeptone*, but it is unknown whether this term represents a complex of various bodies or a single chemical substance. Recent experiments have tended to show that it is a mixture of several substances of much simpler constitution than anything deserving the name of proteid or peptone.

The above description applies to the complete process of tryptic digestion of proteid, but the partially digested proteid resulting from previous peptic digestion, in so far as it has not been previously absorbed, undergoes the later stages of tryptic digestion.

We have at present no means of knowing what fractions of the proteid are absorbed in the various intermediate forms, but we do know that even native proteid is capable of absorption from the intestine, and that digestion merely serves to increase the ease of absorption. It has been shown that the rate of absorption is greater for alkali albumin than for albumins or globulins, and that there is a still greater increase for albumoses and peptones. It is hence probable that a certain fraction of proteid is absorbed as alkali albumin and a still greater portion as albumose, and it is exceedingly unlikely, except when the proteid consumption is largely in excess of the demands of the animal, that any considerable amount passes the stage of peptone. Such a deep-seated chemical change would mean a useless expenditure of energy intended for the tissues in the intestine, where it could merely directly increase the heat production of the animal.

It is similarly probable that a certain amount of the carbohydrate food is absorbed as dextrins, although no dextrin is to be found in the blood of the portal vein. Röhmann finds that even starch disappears from a Thiry-Vella fistula with considerable rapidity, and, since the succus entericus possesses no diastatic action, this must be taken as indicating that the columnar cells are capable of taking up starch molecules. In the entire absence of the pancreatic secretion, also, from one-half to three-fourths of the starch ingested has been found to disappear (Minkowski and Abelmann). Under normal conditions it is, however, probable that practically all the starch of the food is converted into a mixture of dextrin and maltose before absorption.

The only ferment contained in the *succus entericus* is one which has an inverting action upon cane sugar and maltose, and has accordingly been termed *invertin*. This enzyme has a rapid action upon cane sugar and maltose, but is stated to be without action upon lactose. The latter sugar is therefore in all probability absorbed as such, except in so far as it is hydrolyzed in the stomach.

The bile contains no enzymes which possess a chemical action upon any of the food-stuffs. It has recently been shown by the writer that the most important uses of the bile lie in its properties as a solvent for certain substances which are insoluble in water. In this capacity it acts as an excretory agent by dissolving lecithin and cholesterin, both of which are completely insoluble in water; thus rendering possible the removal of these waste products, chiefly of the metabolism of the nervous tissues from the body. Further, the bile, as has been pointed out above, acts as a powerful ally to the pancreatic juice in fat absorption by conferring increased solubility upon the soaps and rendering soluble the free fatty acids.

These solvent properties of the bile depend chiefly upon the bile salts; the practical service of which to the economy is shown by their complete absorption, constituting the so-called circulation of the bile. All the other biliary constituents—except lecithin, which is decomposed and in part reabsorbed in altered condition—are excretory in character and are thrown out in the fæces.

It is noteworthy, in view of the fact that human biliary calculi consist chiefly of cholesterin, that this substance, which is *quite* insoluble in water, only possesses a feeble solubility in solutions of bile salts, amounting to from one- to two-tenths per cent.; it is, therefore, that constituent of the bile which is most likely to be thrown out of solution by any circumstance which either increases the amount of cholesterin to be excreted by the liver, or diminishes the solvent power of the bile, such as a diminution of bile salts. Lecithin is much more soluble and hence is never found in biliary calculi. A five-per-cent. solution of bile salts at body temperature is capable of taking up as much as seven per cent. of lecithin.

The reabsorption of bile salts is practically complete at the ileo-cæcal valve, as is shown by the fact that the reaction from Pettenkofer's test cannot be obtained with the intestinal contents as they escape from a fistula of the small intestine situated immediately above the ileo-cæcal valve.

The fate of the intestinal enzymes during the process of digestion has been much debated. It is certain that ptyalin is completely destroyed by the hydrochloric acid of the gastric juice, and pepsin in turn by the alkali of the intestine; but much doubt exists as to the fate of trypsin, amylopsin, and steapsin. It has been known for some time that the blood plasma possesses feeble amylolytic and proteolytic powers, and it has been inferred that these properties were due to absorption of the ferments from the intestine. It has, however, been shown that the blood plasma is richest in these traces of enzymes during inanition and poorest in them during the period of digestion, which would indicate that the enzymes are taken up by the blood from the cells of the overcharged digestive glands and not absorbed during digestion from the intestine. It is quite certain that all the digestive enzymes are not absorbed before the large intestine is reached, because the contents of the small intestine escaping from a fistula immediately above the ileo-cæcal valve are very rich in both amylolytic and proteolytic ferments, as is shown by their rapid digestive action on both starch and fibrin. Further, it is from the economic point of view exceedingly undesirable that the enzymes should be absorbed by the columnar cells, since they would then, by their activity, interfere with the reverse processes of synthesis of digestion products which goes on in the cell. Hence it is highly probable that the process of selective absorption which reaches its acme in the columnar cells, has so developed in them as entirely to prevent the absorption of these enzymes, which in all probability undergo decomposition in the large intestine.

The absorption of the soluble portions of the food, except in herbivora, is practically completed under normal conditions in the small intestine, for the intestinal contents at the level of the ileo-cæcal valve usually contain neither soluble proteid nor carbohydrate.

In the upper part of the small intestine the secretion of water into the intestine by the digestive glands more than counterbalances the absorption of water by the columnar cells, so that the intestinal contents are fluid, mixed with lumps of undigested food. In the lower third, the absorption of water outbalances secretion so that the contents become thicker, and at the ileo-cæcal valve they usually constitute a thin, semi-solid mass. In the large intestine, the absorption of water still proceeds and the contents gradually take on the consistence of fæces. The degree of dryness of the fæces varies chiefly with the rapidity with which they pass through the large intestine and the avidity of its mucous membrane for the water contained therein. In addition to this continued absorption of water, the chief changes in the contents of the large intestine are due to bacterial action. In the large intestine bacteria flourish abundantly. The ileocæcal valve possesses a peculiar function as a barrier against bacteria, the *modus operandi* of which is entirely unknown to us. As an experimental fact it is well known, however, that the large intestine swarms with bacteria, while they are absent on the upper surface of the ileo-cæcal value. The proteid matter is attacked below the valve by putrefactive bacteria; these set free those volatile bodies which give the fæcal odor to the contents, and they also form stable organic sulphates, which are absorbed and excreted practically unchanged in the urine. Cellulose and other insoluble forms of carbohydrate are also attacked here by bacteria, giving rise to marsh gas and hydrogen which escape by the rectum.

The fæces constitute a very complex residue, which consists in part of undigested débris of food, such as shreds of cellulose, connective tissue, and elastic tissue, and, when the food has been excessive or mastication imperfect, there will be lumps of unattacked food which have escaped the digestive action of the secretions. In addition to this there is a considerable amount of matter not derived from the food, such as detritus from the columnar epithelium, mucin secreted from the intestine, and excretory matter from the bile. The color of the fæces varies greatly and is derived from many sources; it changes with the character of the food, being black or brown, in the case of a flesh diet, from sulphide of iron formed from the hæmoglobin by reduction in the intestine; and light yellow in color, in the case of a vegetable diet, in which the color is due chiefly to bile pigments.

The gases of the intestine indicate that strongly marked reduction processes go on therein; thus, for example, oxygen is entirely absent, and the usual gases are marsh gas, hydrogen, and sulphureted hydrogen. The reducing processes going on are further evidenced by the formation of suphide of iron, as mentioned above, and by the reduction of the bile pigments to hydrobilirubin.

Benjamin Moore.

DIGESTION, DISORDERS OF. See *Stomach, Diseases of,* and *Enteritis.*

DIGITALIS.—Foxglove. The leaves of *Digitalis purpurea* L. (fam. *Scrophulariaceæ*) collected from plants of the second year's growth" (U. S. P.). The British Pharmacopœia specifies "from plants beginning to flower." The German Pharmacopœia requires them to be collected from wild plants in bloom. Other definitions have specified "in full bloom" or even the entire herb in some specified stage of maturity. At present, all these definitions agree in the one important point that the leaves only are employed, the constituents of the flowers and seeds differing in character and properties, and being thus properly excluded. They all agree, moreover, in requiring leaves of the second year's growth, inasmuch as the plant does not flower during the first year. All things considered, the specification of the flowering stage as the time for collection is wise, as the allowance of a very much earlier or very much later period gives no guarantee of the desired quality. There is also little doubt that the wild-grown leaves are usually more active than those of cultivation, though the difference is commonly overestimated.

The plant is very abundant, except in the coldest parts, throughout Europe, besides which it is largely cultivated. It reaches its greatest physical perfection in our northwestern coast States, where it is extensively naturalized along roadsides, attaining a height of ten and even twelve feet. Ordinarily it reaches a height of from two and one-half to four feet, one or more usually simple, erect stems arising from a rosette of radical leaves which replace a similar rosette produced, with the stout conical or fusiform root, during the first year. Upon the stems, the leaves become smaller toward the top, and are finally reduced to large floral bracts. The handsome, drooping, bell-shaped, purple flowers, spotted within with darker purple, are racemed along one side of their stems, generally for more than half their length.

The drug usually comes in bales, sometimes pressed into hard cakes or blocks of different sizes. Some very finely selected leaves are powdered abroad and are imported in small expensive packages, specially for administration in powdered form. The drug is thus described by the Pharmacopœia:

From 10 to 30 cm. long; ovate or ovate-oblong, narrowed into a petiole; crenate; dull green, densely and finely pubescent; wrinkled above; paler and reticulate beneath; midrib near the base broad; odor slight, somewhat tea-like; taste bitter, nauseous.

An infusion prepared with 1 part of digitalis and 10 parts of boiling water, and allowed to cool, has a peculiar odor, turns blue litmus paper red, and, upon the addition of a few drops of ferric chloride T. S., acquires a darker tint, a brown precipitate appearing after a few hours.

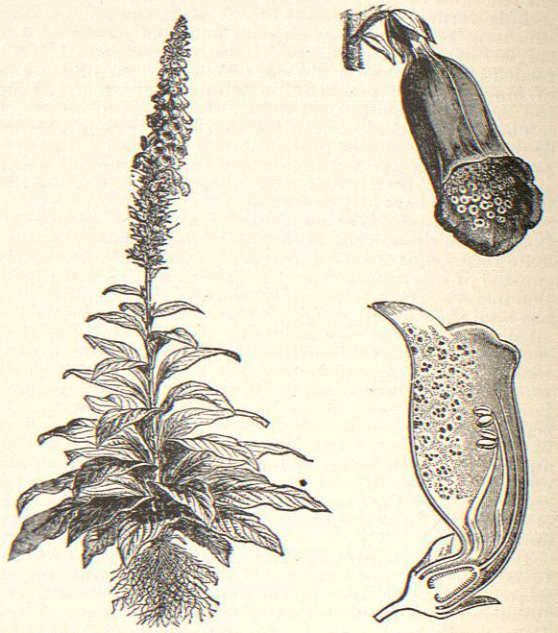

FIG. 1596.—Digitalis Purpurea Linn., Foxglove. Plant in blossom, flower slightly reduced in size, and section of flower natural size. (Baillon.)

The infusion diluted with 3 parts of water becomes turbid on the addition of a few drops of tannic acid T. S.

No other leaf probably offers greater difficulties in the matter of quality selection, and little assistance can be gained from written instructions, success coming only from long experience. This is the more unfortunate, as there is no satisfactory method of assay.

Composition.—The active constituents of digitalis are crystalline glucosides. With them, there occur resin, tannin, gum, pectin, a little sugar and digitaleic acid. Concerning the nature and occurrence of the glucosides, the discrepancy between the statements made by different investigators is so great as to preclude instructive discussion here.

"*Digitalin,*" as dispensed, is very uncertain. Not only is it usually a mixture, but the supposedly chemical body, so called, is not of a uniform character, as supplied by different manufacturers; hence, the only successful way of employing it is to use exclusively the product of the same manufacturer, and learn its therapeutic limitations. It is said by some investigators that true digitalin does not occur in the leaves, but only in the seeds; however, a

substance practically identical with it does occur, and we need not consider this point. Of the formula, Merck says "$(C_5H_8O_2)N$ (?)," and he lists a "German" and a "French" product, both from *Digitalis purpurea,* but the part of the plant not stated. The former is a yellowish-white powder, soluble in water and alcohol. The dose is given as 0.001 to 0.002 gm. (gr. $\frac{1}{64}$–$\frac{1}{32}$), three or four times a day, and not to exceed gr. $\frac{1}{3}$ daily. The French article is similar, soluble in alcohol, but only in 2,000 parts of water. The dose is gr. $\frac{1}{250}$, which may be increased to a maximum of gr. $\frac{1}{40}$ daily. Both these solutions have the characteristic action of digitalis upon the heart.

Digitoxin ($C_{21}H_{32}O_7$?) is the most abundant, as well as the most active constituent. It is a white crystalline powder, soluble in alcohol, but not in water, although, by virtue of the associated bodies in the leaves, it is extracted by the infusion. The dose is gr. $\frac{1}{250}$–$\frac{1}{125}$ three times a day, and it is recommended that chloroform ♏ij., alcohol fl. ʒ i., and water ℥ iss., be taken with it. The maximum amount for the day is gr. $\frac{1}{32}$. As an enema, gr. $\frac{1}{80}$, with alcohol ♏x. and water fl. ℥ iv., is recommended.

Digitonin ($C_{31}H_{52}O_{17}$?). The presence of this in the leaves is denied. However, it is similar to saponin, and in the doses of digitalis its action is not appreciable. The same is true of digitin $(C_4H_9O_2)N$. *Digitalein* is a mixture.

In accordance with, or in spite of any, recognized facts regarding the constituents of digitalis, it is true that an alcoholic preparation, while markedly diuretic, does not exert so great a direct stimulant or irritant action upon the kidney as does the infusion.

Action.—The different ways in which digitalis acts upon the organs may first be considered.

1. It stimulates the muscular fibres in the cardiac and arterial walls, thus increasing cardiac force and in a double way raising blood pressure.
2. It stimulates the nerve tissues in the heart (at least the nerve endings, the action upon the ganglia being doubtful) and in the arteries, thus increasing the above-mentioned effects, but at the same time beginning to slow the heart by stimulating the ends of the vagus.
3. It stimulates the centres in the brain and cord, thus greatly increasing the slowing of the heart and still further increasing its force.

As the effects of the drug are such as I have just enumerated, it follows that well-regulated doses will restore rhythm to an irregular heart. It is probably due to this stimulation of the vagus that digitalis relieves cardiac irritability resulting from over-exertion. When high fever exists, this slowing of the heart is less apt to take place. The effects of the above-described actions have to be very carefully considered in determining the use of the drug. Its action is characteristically slow in coming on, requiring usually several hours, and the effects are similarly slow in passing off, so that when great promptness is required, digitalis is not available. One feature of the slow heart beat produced by this drug is an extension of the space required in the diastolic condition; hence when there are great accumulations of fluid encroaching upon the heart space, we must be cautious in our use of digitalis.

A more important consideration is the difference of digitalis from other cardiants in its powerful stimulation of the arterial walls. This prevents the heart strengthening from resulting in a clear gain (especially in view of its slowness), for resistance is at the same time increased. Since the increased heart action depends upon the muscular cardiac walls, it cannot so well take place when these are weakened by dilatation or fatty degeneration, or when there is aortic regurgitation, for here we simply increase resistance more than we do heart strength and thus favor backing up of the blood into the heart. Unless we can then relax the vessels in some way, it is better to substitute some other cardiant. Recent experiments made on pigs by Hare go to show that by administering digitalis carefully, increasing the dose gradually until large amounts are taken, we may bring about a great and permanent increase in the size and quality of the muscle of the healthy heart. If it shall be found, upon further trial, that this same effect can be produced in the case of a dilated heart, it can readily be appreciated how far this result will exceed all our past anticipations with regard to the usefulness of digitalis. The next most important effect of the drug is upon the kidney. It is a recognized principle that increased blood pressure favors increased renal secretion, which alone would account for the diuretic properties of digitalis; but in addition, there is a direct renal stimulation effected by irritation and by locally contracting the vessels, thus inducing an even greater local increase of blood pressure. This occurs the more easily because the substance is almost wholly excreted through the kidney. This presentation of the modus operandi of the drug is subject to certain modifications. The excessively stimulating effect upon the kidney often results in an over-contraction of the renal vessels, which checks secretion. As this state passes off, a profuse secretion comes on very suddenly. If this change does not promptly take place, the digitalis checks its own excretion and continues in the circulation, becoming cumulative in a way very different from its cumulative action upon the heart muscle already considered, and is liable to become poisonous. In a state of health, the diuretic effect of digitalis is not usually pronounced, unless the blood pressure is unusually low (Brunton).

The other actions of digitalis are not important, except that it is very likely to irritate the stomach and intestines; this is especially true when the drug is given in the form of the infusion. Such irritation may add to the nausea or vomiting which is often caused by disturbance of the cerebral circulation; it may also produce a laxative, or even a purging effect. The cerebral disturbance may also cause dizziness, headache, disordered sight, and hearing. The uterus is stimulated. The slight antipyretic effects which digitalis produces are probably dependent upon the lessened circulation induced by slowing of the heart.

Uses.—We cannot do better than to reprint Beaumont Small's account of the uses of digitalis, as given in the supplement to the last edition of this work.

"Digitalis maintains its position at the head of heart tonics. In England and America authorities are as one on this point. On the continent they are the same. Dujardin-Beaumetz assigns it the first rank and calls it 'the type of heart tonics'; Professor Nothnagel places it above all other heart tonics, and Herr Fürbringer says, 'the sovereign diuretic in cardiac disease has been, and still is, digitalis.' Continued use has confirmed the confidence placed in it, and the innumerable rivals that appear serve only to bring its superior qualities into bolder relief. Not much has been added to the uses of this remedy, but we know more definitely its proper sphere, and apply it with more precision to the conditions in which it will prove of value.

"In organic disease of the heart the guide for its use is the state of the compensatory action of that organ. It is not given as a remedy for the defective valves, nor with the expectation of benefiting any diseased condition of the organ; it is simply a stimulant and tonic to the muscular tissue. So long as the heart is able to overcome the impediment to the circulation and maintain a free flow of blood, nothing is to be gained by the use of the drug, but, with the earliest symptoms of failing power, its administration must be commenced. The system responds quickly to the first indication of this loss of compensation, the heart beats more feebly and quicker, the pulse becomes irregular, a slight degree of dyspnœa is noticed, and œdema of the feet and ankles begins. In such conditions the beneficial action of digitalis is most marked. The heart beats more slowly and forcibly and propels the blood onward, the arteries become filled, the engorged veins relieved, and the equilibrium of the circulation is re-established. This slower action of the heart allows of a prolonged period of diastole, during which it is at rest and recuperating; the succeeding contraction is rapid and strong, due to the renewed strength and stimulating action of the remedy.