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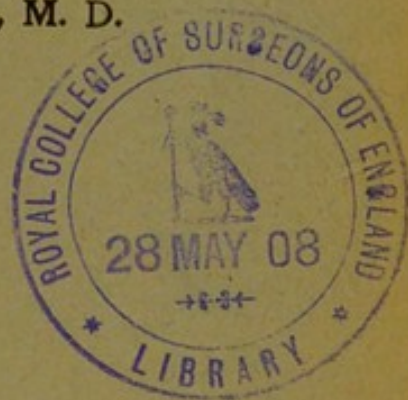
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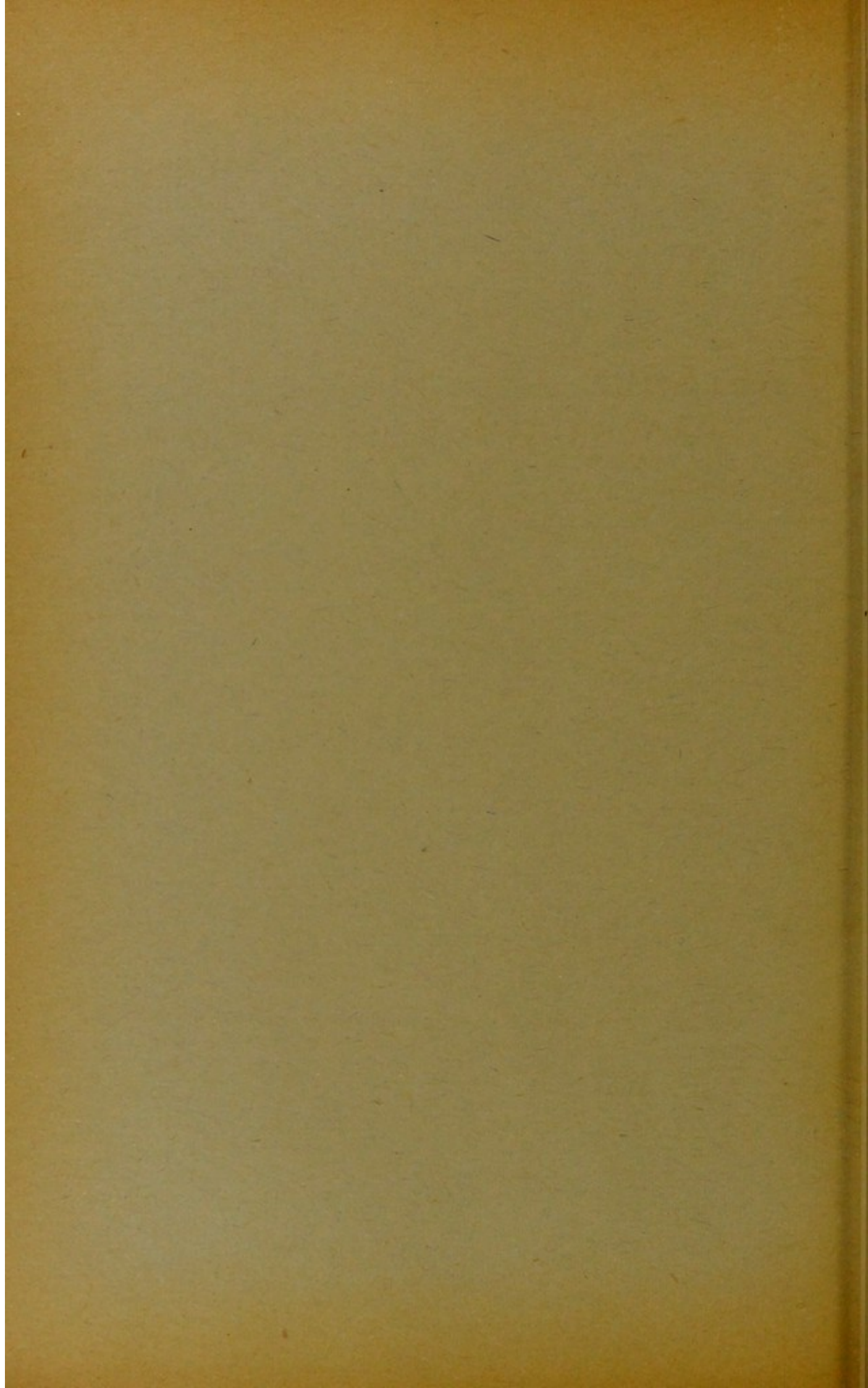
INDICANURIA A DANGER SIGNAL! ITS
VARIETIES AND TREATMENT.

BY

WILLIAM HENRY PORTER, M. D.



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INDICANURIA A DANGER SIGNAL! ITS VARIETIES AND TREATMENT.*

BY WILLIAM HENRY PORTER, M.D.

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The main object of this paper is to consider the diagnosis and treatment of the more common types of indicanuria as they are observed clinically and especially the changes found in the urine.

While the presence in the urine of the substance called indican or indoxyl-potassium-sulphate has been known to the profession since its discovery by Prout, in 1840, its importance in clinical medicine and surgery has only comparatively recently been appreciated. Indeed, its full value in diagnosis and prognosis is even now not as generally recognized as it should be.

Of itself, indican is only a symptom; yet, when the clinical phenomena and the changes in the system occurring in connection with it are correctly interpreted, it becomes one of the chief signs of disturbance in metabolism. It has been demonstrated by many observers that indican, when found in the urine and considered separately, indicates but one thing, namely, that somewhere in the animal economy—*nearly* always in the alimentary tract—proteid elements are undergoing putrefactive decomposition. Although some investigators regard small amounts of indican as normal, this is very misleading, because no one can say with accuracy at what percentage the normal gives place to the abnormal. On the other hand, there can be no question between its absence and its presence. Under no circumstances can putrefactive fermentation be considered physiological. Even the slightest trace of indican in the urine is abnormal.

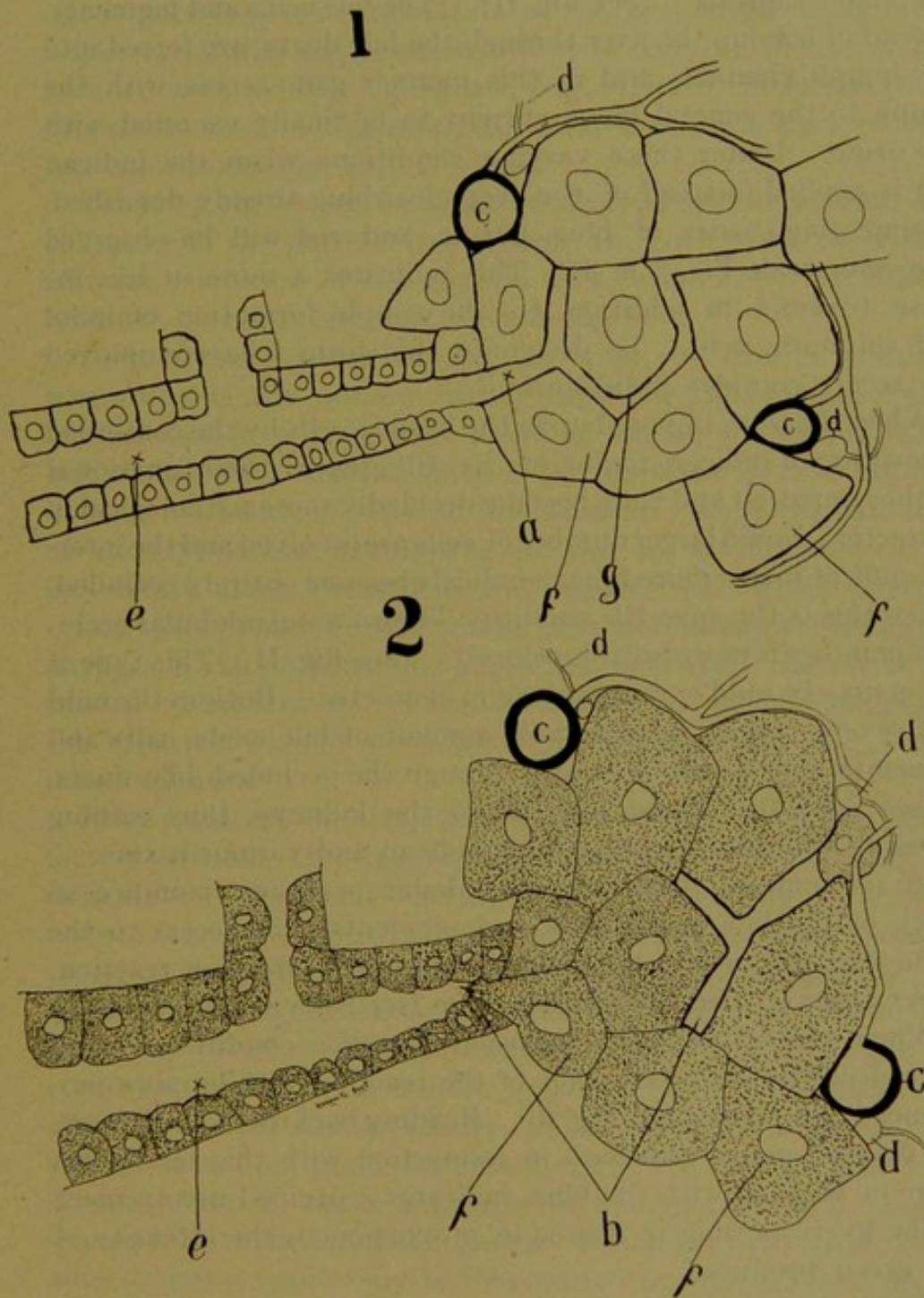
As has already been stated, indican is, in the vast majority of cases, the result of putrefactive changes occurring in the proteid elements of the food-stuffs passing through the alimentary canal. Under these circumstances the process is not, strictly speaking, an autoinfection but an extrinsic one or, as it were, an infection from outside the body. On the other hand, it is unquestionably true that in a *small* percentage of the cases putrefactive changes occur in the proteid constituents of the

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body. A good illustration of this is observed in putrid empyemas gangrene of the appendix accompanied by considerable putrid pus, etc. The process under these conditions is, correctly speaking, an autointoxication. The amount of indican reaching the urine directly from putrefying pus is generally *very small* compared with that derived from the intestine, and the two are often confounded. It is further evident from both clinical and chemical analysis that putrefactive decomposition of the proteid elements may be a somewhat simple or quite a complex process. In the simple process the products of decomposition are indol and sulphuric acid alone, which, when joined to a potassium atom, form indoxyl-potassium-sulphate. In the complex process, in addition to the two substances already mentioned, innumerable more or less toxic by-products are formed. These by-products, when introduced into the general circulation with indican, give rise to varying degrees of toxemia.

When indol and sulphuric acid are the chief products of proteid decomposition, the ordinary test for indican in the urine gives a sharp, deep indigo-blue reaction as contrasted with a pure white when the same test is applied to normal urine (see color scale, Fig. 1 & 2, Plate I.).

Not infrequently there is a still more complex transmutation of the proteid elements. When this occurs an almost endless variety of toxic products are formed either as the result of a more complex oxidation reduction of the proteid molecule or by an isomeric change in its molecular structure. Some of these toxic products are in the form of oxidation reduction substances, while others are in the form of toxalbumins. No matter how they are formed, or what their nature when these toxins gain access to the general circulation they produce various abnormal changes in metabolism and cause an almost endless variety of symptoms. They may break up the hemoglobin of the blood and thus augment the coloring matter in the urine. In other instances they reach the liver through the enterohepatic circulation, and are thus brought into direct contact with the hepatic cells, which have the power to take up these toxic molecules from the blood stream and transmute them into a less toxic form. When this occurs the hepatic cells are often overtaxed; they lose their normal nutritive activity and become granular, swollen and sluggish in action. In this condition



No. 1.—Normal Liver. *a*, internal end of bile radicle patent; *e*, bile duct lined by normal cells; *c*, intralobular blood vessels; *d*, small bile ducts outside the lobule; *f*, hepatic cells in the acinus; *g*, basement substance between hepatic cell and lymphatic spaces.

No. 2.—Abnormal liver, showing changes common to intralobular jaundice; *e*, primary bile radicle; *b*, points to occluded bile radicle by swollen cells; *f*, swollen and granular cells in acinus; *c*, blood vessels in acinus; *d*, bile ducts outside the acinus.

FIG. II.

some of the hepatic cells often occlude the mouths of the internal biliary radicals. (See Fig. II). The bile acids and pigments, instead of leaving the liver through the bile ducts, are forced into the lymph channels and in this manner gain access with the lymph to the general blood current to be finally excreted with the urine. Under these varying conditions when the indican test is applied, instead of the deep clear blue already described, innumerable shades of blue, purple, and red will be observed (see color scale Fig. 3 & 4). This indicates a more or less intense toxemia in addition to the simple formation of indol and sulphuric acid. To designate this form I have employed the term "complex indicanuria."

When the work imposed upon the hepatic cells by the continued absorption of indican, toxins, etc., is still greater, their function is further impaired and they become decidedly more pathological in character. Now a larger number of cells are involved and the internal ends of many more biliary radicals become entirely occluded. When this is the case, the condition known as intralobular occlusion jaundice is more fully developed. (See Fig. II.) This type of lesion may be mild or quite severe in character. Both in the mild and severe types a considerable amount of bile acids, salts and pigments, which cannot escape through the occluded bile ducts, passes into the blood and on to the kidneys, thus gaining access to the urine together with indican and various toxins.

In pronounced forms of intralobular occlusion jaundice so much of the bile acids, salts and pigments gain access to the urine that the indican test gives a decidedly greenish reaction, either alone or blended with the blue (see color scale, Fig. 5).

When the intralobular occlusion jaundice condition is still more decided, the green color of the reaction will be more pronounced (see color scale, Fig. 6). Reading backwards, as it were, the decided green observed in connection with this test, when alone or blended with the blue, indicates a decided involvement of the liver, varying in degree in proportion to the intensity of the green produced.

When the intralobular occlusion condition is very extensive, the color obtained upon application of the test is often very intense green or bluish black, in some instances being almost black (see color scale Fig. 7.).

When potassium iodide is being taken, this same test gives a

red color (see color scale Fig. 8), but if, at the same time, there is much putrefactive fermentation in the proteid elements in the alimentary canal the reaction will show varying shades of blue blended with red (see color scale, Fig. 9); or if the fermentation process is mild in character the color may be a decided pink (see color scale, Fig. 10).

Thus, by these reactions can be determined the amount and character of the putrefactive process, the toxicity of the system and the condition of the hepatic cells, even when the color is modified by the presence of the iodides.

From these observations we find that, by careful comparative study of the urinary findings and the clinical phenomena as observed in a very large series of cases—comprising many hundreds—the sharply defined color reactions as here outlined indicate well-defined types of indicanuria. While the oxidation of indoxyl-potassium-sulphate in the urine into indican is incorrectly diagnosticated as the disease, the correct interpretation of its presence enables us to fully understand the abnormal changes in the proteid elements in the alimentary tract or in the tissues. Furthermore, it furnishes data by which changes in the hepatic cells and in metabolism in general can be correctly diagnosticated.

Briefly stated, the deep blue alone indicates a simple putrefactive process; the varying shades of blue, purple and red indicate a higher and varying degree of toxicity. The pronounced green denotes a mild form of intralobular occlusion jaundice in addition to the putrefactive and toxic process; the darker green, greenish black and blue-black a pronounced occlusion jaundice together with the putrefactive and toxic condition; a still more intense green or black, still worse condition, but of a similar nature. The red alone indicates that iodides have been taken into the system; red blended with blue or pink, that in connection with the iodides there is a varying degree of putrefaction and toxemia. Much finer shades of difference, however, can easily be determined by any one who makes a close study of these urinary reactions in conjunction with the clinical phenomena.

Another fact that should never be overlooked is that the associated toxicity of the system may often be greater than the intensity of the test indicates. This is particularly the case

when the indoxyl-potassium-sulphate passes out with the feces while the toxins continue to be absorbed. Under such circumstances a slight checking of the bowel activity will bring clearly to light the exact situation.

The following method for determining indican in the urine and the different types of indicanuria is the one which, after several years of careful observation, the author has found to be the most reliable:

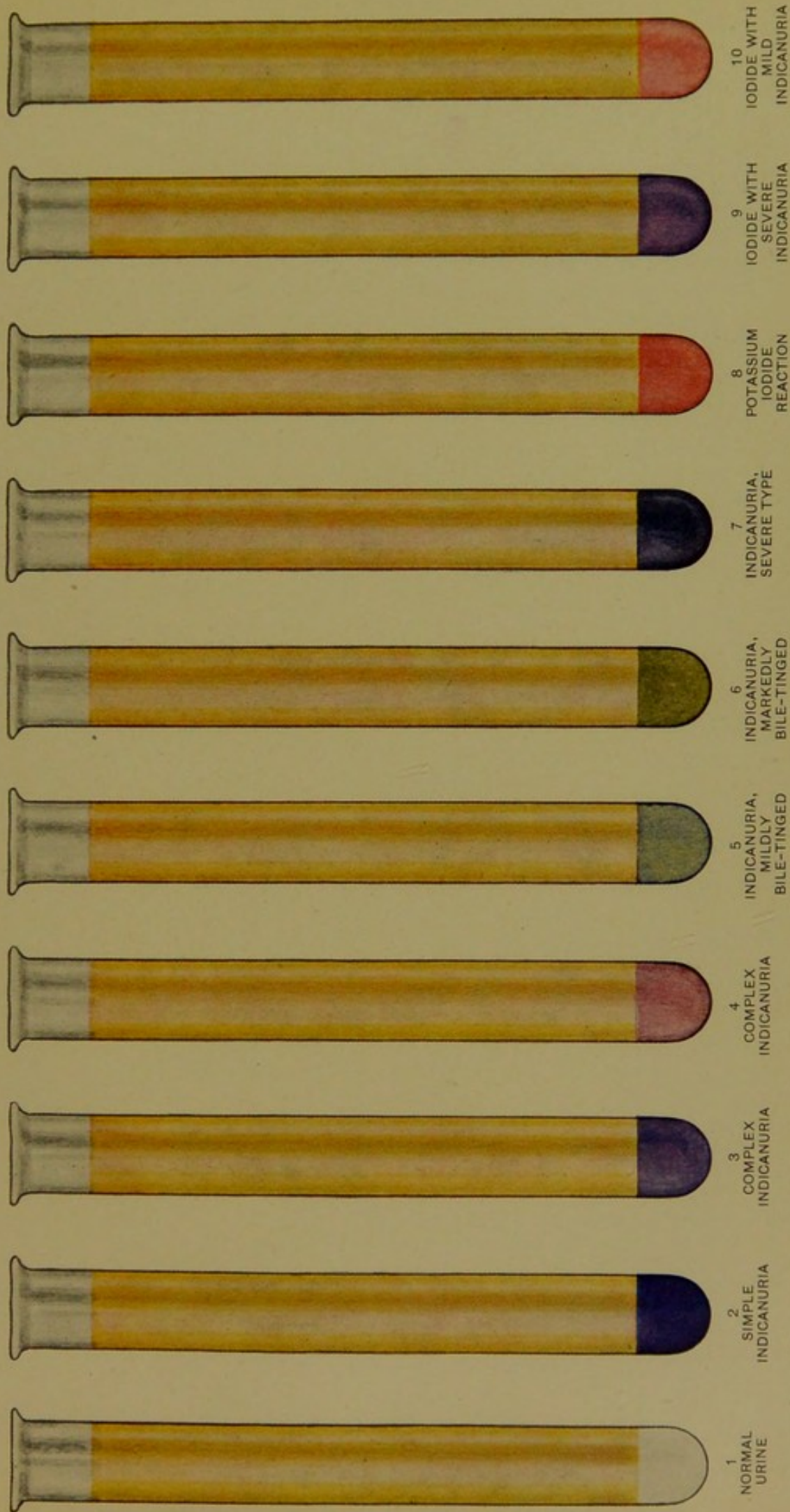
Place in a test tube equal quantities (10cc. of each) of urine and chemically *pure concentrated* hydrochloric acid. To this mixture add three (3) drops of a one-half ($\frac{1}{2}$) per cent. solution of potassium permanganate. Then add a small portion of chloroform, one or two more drops of the permanganate solution and a few drops more of chloroform, or a total of five (5 c. c.) of chloroform, and shake vigorously for a few seconds. (See Fig. III.).

1. In the absence of either extrinsic or intrinsic putrefaction the chloroform will settle to the bottom of the fluid in the test-tube and remain pure white (see color scale, Fig. 1). This indicates a perfectly normal state.

2. If there is a simple putrefactive process of either form with little or no toxic infection, but in which the indoxyl-potassium-sulphate has found its way into the urine, there will be formed first upon addition of the acid and permanganate solutions, a purplish cloud in the fluid in the test tube. Upon addition of the chloroform the purple quickly gives place to a decided deep indigo-blue (see color scale Fig. 2). This is due to a precipitation of small particles of indigo-blue resulting from the oxidation of the indoxyl-potassium-sulphate into the substance called indigo and its precipitation by the chloroform. In the absence of all other pigments and toxic products the deposited chloroform and indican remain deep blue in color. This result is indicative of simple indicanuria.

3. When pronounced toxemia is associated with the putrefactive process, there is often a breaking-up of the hemoglobin and the formation of a red pigment; or there may be some occlusion to the internal ends of the bile ducts. When this is the case the bile pigments, acids and salts re-enter the blood and finally the urine. Various toxins also enter to the urine. When this is the case the pigments or toxins interfere with this test reaction as just described; that is to say, these substances are

INDICAN COLOR SCALE





added too or precipitated with the indigo produced by the oxidation reduction of the indoxyl-potassium-sulphate. Now, instead of the sharp and distinct blue reaction, a dirty blue, purplish or reddish color is obtained, the shading in color depending in a large measure upon the form of pigment or toxin entering into the combination, (see color scale, Figs. 3 and 4). This result indicates a more or less complex toxemia in addition to the simple indicanuria.

4. With a more marked change in the hepatic cells and the development of a somewhat pronounced occlusion of the internal ends of the bile ducts, varying shades of green will be noticed in the deposited chloroform (see color scale, Fig. 5). This always indicates that a considerable amount of the bile pigments, acids and salts have reentered the blood and been excreted with the urine. This is especially so in reference to the biliverdin.

5. With a still more pronounced hepatic involvement the color will be a still more pronounced green (see color scale, Fig. 6).

6. When the involvement of the liver is still greater the reaction will be still more green or it may assume deep green or bluish black. Where the putrefactive process and the liver involvement are both very pronounced, the deposited chloroform will be almost black, (see color scale, Fig. 7).

7. When the iodides are taken and there is no putrefactive fermentation, the deposited chloroform instead of being white, as under normal circumstances, is cherry red in color, (see color scale, Fig. 8).

8. If in conjunction with the use of the iodides there is also pronounced putrefactive action, the deposited chloroform will be decidedly violet in color, (see color scale Fig. 9).

9. If the putrefactive process is less intense, the deposited chloroform will assume a more pink color, (see color scale, Fig. 10). The shade of color in the two last reactions, as in all the other tests, is governed largely by the amount and variety of the extraneous pigments added to the indigo.

To determine the perfection or imperfection of oxidation reduction, the total output of urea must be accurately estimated. We must estimate also the precise amount of overproduced uric acid. This is best accomplished by the author's method as

TEST FOR INDICAN



Take 10 C.C. of urine, 10 C.C. hydrochloric acid and 5 drops of $\frac{1}{2}$ % solution potas. permangan. and shake. Then add 5 C.C. chloroform and shake. Purple coloration followed by deposit of blue pigment shows presence of indican.

TEST FOR OVERPRODUCED URIC ACID

After boiling the upper strata of urine add a few drops of 4% acetic acid. Let it stand for 3 or 4 hours, after which the overproduced uric acid will crystallize out just beneath the surface of urine in test tube.



Uric Acid Crystals

FIG. III.

given in Fig. III. In this Fig. where the term "few drops" used it means from five to ten.

The presence and amount of the oxalates, either alone or in combination with an excessive output of the earthy phosphates, is another important point to be determined, as it indicates faulty metabolism located chiefly in the nervous mechanism.

As only seventy three per cent. (73%) of the nitrogen is eliminated from the system by or through the kidneys and as there is always more or less oscillation in the amount eliminated through the kidneys and the other organs that excrete nitrogen, it is even more essential to determine the overproduction of uric acid, the oxalates and earthly phosphates than that of the urea alone; because they are the true indicators of imperfect oxidation reduction. Therefore, if we make due allowance and study carefully the imperfect products of oxidation reduction we can come marvellously near the exact state of the metabolic process.

Owing to the great diversity of factors entering into the production of this condition of putrefactive fermentation and its associated toxemia, together with its very complex chemico-pathological nature, it calls for consummate skill in the science of therapeutics to cope successfully with this problem. It is without question the largest and most difficult condition in medicine to treat successfully that confronts the general practitioner or the specialist. It is one that is met not only daily but many times daily by all who practice medicine. The successful management of these cases demands a concise knowledge of all the clinical phenomena as well as an accurate understanding of the laws of chemistry, physiology and pathology entering into the production and maintainance of these conditions. A clear and intelligent understanding and application of all these laws, and treatment based thereon, will, whenever the patient can be absolutely controlled and made to do perfectly his or her part, invariably result in phenomenal success.

To be successful in the management of this great class of disturbances in metabolism, each case must be separately analyzed, the type and its exact cause determined with absolute precision.

The three fundamental factors that predispose and lead up

to a state of the alimentary tract that will favor the growth of the pathogenic bacteria, which is the essential and final cause of the formation of the indoxyl potassium sulphate and its associated toxins, are:

First, eating and drinking too much or taking food of faulty composition.

Second, a decrease in the amount and perfection of the digestive secretions.

Third, a faulty innervation of the glandular system taken as a whole.

Viewed in this light there are four well defined things to be accomplished, namely, the arrest of the action of the bacteria, regulation of the diet, re-establishment of a normal state of the digestive system as regarded the perfection and action of their secretions, and the establishment of a perfect innervation to the glands.

While the action of the micro-organisms is the essential etiological factor, the conditions that makes possible a soil suitable for the growth and action of the bacteria must be considered first. We must determine which of the etiological factors is the predominating one and direct our endeavors primarily in such manner that they will most effectually overcome the defects in the order of their importance.

Regulation of the diet is absolutely essential. We must select a diet that can be most easily digested and utilized with the least expenditure of digestive energy. It must be also as free as possible from all abnormally fermentable and irritating substances. It must contain also the requisite amount of inorganic elements rightly proportioned, just sufficient proteid material to supply the requisite amount to make good the general wear and tear of the system, and still leave a surplus sufficient to repair whatever damage may have been wrought in the various protoplasmic structures of the body prior to instituting treatment.

Within the past few years Professor Chitenden has apparently proved that by using about one-third the proteid material ordinarily considered requisite, the highest degree of health can be secured and maintained. My experience in the management of this class of disturbances, and it has been a pretty large and extended one, has been that at least 150 grams of proteid

must be utilized daily to secure the desired results. And until the patient can be brought to the point of being able to digest and utilize this amount of proteid very little improvement is noticed.

Another exceedingly important point in connection with the regulation of the diet is the supply of starches, sugars and fats. The supply of the two classes must be so perfectly adjusted that the heat energy derived from these two classes will yield a perfect physiological balance in accord with the exact economic demands of the animal economy. If sufficient heat energy is not supplied to call into play the requisite nerve energy essential for a perfect utilization of the proteid elements, imperfect utilization of the proteids follow. On the other hand, too much heat production may be detrimental, but a lack in amount produced is far the most damaging. The source of the heat production is another point of great importance. My experience is that too much starch and sugar is used and too little fat. By reversing somewhat the amount from what is generally given much better results can be obtained.

The fourth point in connection with the diet is the supplying of food which contains a requisite amount of the iron and phosphorous bearing elements, or the protonuclein and hemoglobin forming substances.

To secure a perfect adjustment and utilization of these four classes so as to perfectly meet the defects in each case and in the different types of indicanuria is often a task of consummate magnitude. Unless this task is perfectly accomplished we have not completely removed the error in diet which is acting as the primary etiological factor. And until this causative factor is removed recovery cannot be secured.

The form of diet which yields the best results is the well regulated mixed diet, but one in which the animal class always predominates, while the vegetable class is kept well in the minor quantity. In the latter class the green vegetables should be liberally supplied. Substituting the vegetable for the animal class will often dispel the indoxyl potassium sulphate from the urine, but at the same time reduces the nutritive activity of the system to a very low ebb. Hence, if the most thorough and satisfactory results are to be obtained in the management of these pathological conditions, so far as my experience goes, the animal foods must always predominate.

The fruits both raw and cooked should as a rule be excluded. The same is true of all highly fermentable and irritating substances.

This brings us to the consideration of the second etiological factor or defects in the digestive secretions and their management. Here we have another gigantic problem to contend with, one that may be classed as the most difficult of all to successfully handle. It is one also that must be reckoned with in all the different forms and types of indicanuria. Defects in the digestive secretions may act primarily or secondarily as the chief element in making possible the damaging effects of the pathogenic bacteria.

While it is known full well, that the different ingredients of the digestive fluids are not in any sense antiseptic; yet on the other hand it is equally true that when the digestive secretions are fully produced both as regards quantity and quality they do inhibit positively, in the alimentary canal, the action of micro-organisms detrimental to the maintenance of a normal state of the digestive system. Therefore, it is absolutely essential in all cases and types of indicanuria to determine to what extent the defect in these secretions is acting as an etiological factor, or one that is aiding in the maintenance of the putrefactive process in the intestinal tract. As deterioration in the perfection of the digestive secretions acts to a greater or less extent in all cases, this defect must receive attention all through the course of every disturbance in metabolism that we are called upon to treat.

The determination of just which secretion or which ingredient of a given secretion is deficient in amount or activity is often no easy task. It is a pretty generally recognized fact, however, that when there is a disturbance in metabolism with defective oxidation, a condition usually associated with indicanuria, there is necessarily a decrease in the production of sulphuric acid by the epithelial cells of the gastric mucous membrane. This naturally means as a necessary sequence a diminished production of hydrochloric acid, and as the hydrochloric acid is needed quite as much if not more for its reflex stimulating action in exciting the pancreatic secretion, than for its syntonizing action upon the proteid constituents of the stomach content, it is absolutely essential that this defect be made good. This

can be accomplished by the administration of some dilute hydrochloric acid, or any of the other mineral acids, for all of them result ultimately in the production of hydrochloric acid in the stomach (see Table III). Hydrochloric acid being the natural stimulus to the pancreatic secretion is the form of acid to be selected first. At times, however, it is not well borne by the stomach; then some other form must be chosen.

The ordinary test meal used for determining the presence or absence of hydrochloric acid is often misleading, because it is an abnormal form of stimulation and tends to excite an abnormal outpouring of hydrochloric acid, and therefore to say the least, the result is not a true but misleading register of the stomach activity, in disturbances of metabolism. Deductions made in this manner are on a false premise.

The administration of pepsin is of comparatively little value and especially so when we remember that only one ninth of the digestive work is accomplished in the stomach under the best of circumstances. That is to say one third of the proteids are peptonized in the cavity of the stomach the other two thirds being so transformed after they have left the gastric cavity.

Having passed out of the stomach and into the intestinal canal we usually find a decreased supply of pancreatic secretion and of its contained ferments trypsin, lipase, and amyllopsine. Now we come to a new point as it were. The pancreatic secretion has been shown to be absolutely essential to excite the secretions of the mucus membrane of the intestinal tract and bring forth its contained ferments, the enterokinase from the duodenal glands and the erepsin a little further down. As it has been further shown that the ferments of the pancreatic fluid are in themselves inactive unless excited into action by the ferment enterokinase it is doubly essential that we bring about the largest possible flow from the pancreatic gland compatible with physiological laws. When this cannot be done this deficiency can be made good in a large measure by the administration per os of pancreatic extracts. Just here another very important fact must never be lost sight, to wit, the necessity for a goodly supply of bile. Bile is absolutely essential in connection with these processes on account of its inhibiting action upon the ferment action of the pepsin which is rapidly

TABLE III.

THE THERAPEUTIC ACTION OF MINERAL ACIDS.

THEIR REACTIONS IN THE ANIMAL ECONOMY.

Arranged by WILLIAM HENRY PORTER, M.D.

ACID USED.	PLACE OF REACTION.	REACTIONS.
Nitro-hydrochloric.....	Stomach.....	$(2\text{H}_2\text{O} + \text{NOCl} + \text{Cl}_2) + \text{NaCl} = 4\text{HCl} + \text{NaNO}_3$
	Intestine.....	$4\text{HCl} + 4\text{Na}_3\text{PO}_4 = 4\text{NaCl} + 4\text{Na}_2\text{HPO}_4$
Hydrochloric.....	Intestine.....	$(\text{HCl}) + \text{Na}_3\text{PO}_4 = \text{NaCl} + \text{Na}_2\text{HPO}_4$
Nitric.....	Stomach.....	$(\text{HNO}_3) + \text{NaCl} = \text{HCl} + \text{NaNO}_3$
	Intestine.....	$\text{HCl} + \text{Na}_3\text{PO}_4 = \text{NaCl} + \text{Na}_2\text{HPO}_4$
Sulphuric.....	Stomach.....	$(\text{H}_2\text{SO}_4) + 2\text{NaCl} = 2\text{HCl} + \text{Na}_2\text{SO}_4$
	Intestine.....	$2\text{HCl} + 2\text{Na}_3\text{PO}_4 = 2\text{NaCl} + 2\text{Na}_2\text{HPO}_4$
Phosphoric.....	Stomach.....	$(\text{H}_3\text{PO}_4) + 2\text{NaCl} = 2\text{HCl} + \text{Na}_2\text{HPO}_4$
	Intestine.....	$2\text{HCl} + 2\text{Na}_3\text{PO}_4 = 2\text{NaCl} + 2\text{Na}_2\text{HPO}_4$

flowing into the duodenum. The necessity for inhibiting the pepsin ferment action is that so long as the pepsin remains active it strongly inhibits the action of the pancreatic ferments and that of the enterokinase.

Taking all these facts together it is easy to see that at just this point in the digestive tract and its activities, we meet one of the most complicated and yet active processes in the whole course of the digestive act. Secretions and ferments stimulating the secretion and production of ferments, inhibiting and exciting each other into chemical activity, until chemical changes are wrought in the food stuffs with a swiftness and accuracy that is almost beyond comprehension. One which in simple test tube and laboratory experimental work often seems to be absolutely contradictory and worthless for practical clinical application. Yet when all that we do know is intelligently applied at the bedside marvelous results are not infrequently secured. This is especially true in connection with the internal administration of the pancreatic and biliary extracts. Some claim that these substances are destroyed in their passage through the stomach. If we remember, however, that the pancreatic ferments act in an acid, neutral and alkaline medium, and also that it acts best in the latter we can readily see that it can pass through the stomach without losing its power for good. Again, it should be remembered that these ferments have no ferment action in themselves, but require the catalytic action of the enterokinase to excite their activity, hence it is easy to see how an error might be made in reference to their passage through the stomach. Another point of interest in connection with this very complex phenomenon, is the inhibiting effect of the bile, upon the inhibiting effect of the pepsin upon the pancreatic ferments, and so on through the series of actions and reactions. All of which indicates to my mind that when the two bile and pancreatic extracts, are given in combination the one carries the other as it were, safely through the stomach. We have already found that the contained ingredients of the pancreatic secretion are absolutely essential to call forth the ferment produced in the duodenum, and which is the catalytic element which excites the pancreatic ferments into activity. Until it has been demonstrated beyond a question of doubt that the pancreatic ferments are inert, after passing through the stomach and have had sufficient

enterokinase added thereafter to set them in motion we are still justified in the belief that they do safely make the transit of the stomach and are valuable therapeutic agents. Again in reference to their activity in an acid medium, it must be remembered that the contents of the duodenal canal must be more or less highly acid for a long time after the stomach content begins to flow into the duodenum, and we know that this must be so to call forth the largest pancreatic secretion.

Therefore, it seems to me that we are fully justified by facts and experiments and from an abundance of clinical evidence in the assumption that to overcome the deficiencies in the digestive processes in the intestinal tract, the best results can only be secured by the administration per os of substances which approach as nearly to those normally formed in the digestive tract. And these are inspissated bile and pancreatic extract. So far as the author knows no reliable preparation of enterokinase or erepsine has been produced for practical internal administration. If such was the case they also should be added. On the other hand the bile and pancreatic extracts have been in general use for many decades. So that an abundance of experimental and clinical evidence is at hand which furnishes a large amount of proof that establishes beyond a question of doubt their efficiency.

These substances can be administered in powder, capsule or liquid form. As the first and the last are apt to be decidedly unpalatable, the capsule form is the one in common use. In young children and in adults who cannot swallow pills or capsules it is no easy matter to introduce these often much needed substances into the intestinal tract.

While it is claimed by many observers that the bile is purely an excretion and hence of little or no value as a digestive agent, it is equally true, from a clinical standpoint, that it is almost impossible to secure the desired results in the management of this class of cases without its addition to the alimentary tract. While it has no well defined unorganized enzyme, it, as we already noted, inhibits the action of the pepsin ferment, when that ferment reaches the duodenum. Further than this it appears to aid greatly the activity of the pancreatic ferments. It has also been proven, beyond a question of doubt, that the administration of bile even in moderate amounts augments greatly the

production of bile by the liver, both as regards quantity and perfection of composition. Such a result can be brought about by its power to increase the perfection of the digestive act and by a more rapid absorption of the digested nutritive pabulum. Thus supplying to the liver a larger amount of proteid material out of which the liver cells can oxidize the proteid molecules into the nitrogenous ingredients of the bile. In the absence of well defined enzymes in the bile as it flows from the liver, into the intestinal canal its valuable action in connection with digestion and absorption must reside in its contained bile acids, for they are its most active chemical constituents. These acids act either singly in the acid state or by being combined into salts, probably in both forms. The action may be a purely chemical one or it may be of the so-called catalytic nature, their presence exciting other substances into activity or increased activity. These deductions have come about largely by the study of the bile obtained through biliary fistulæ, both in animals and human subjects, the latter of which are the most valuable. And also at the same time by noting closely the changes in the oxidation products in the urine as a result of the administration of the bile and its discontinuance under exactly similar conditions. In this manner the exact physiological and therapeutic value of bile and its extracts can be easily determined. In a similar manner the same results have been obtained in relation to the pancreatic secretion, although it is not so easily done. Reasoning by analogy, however, and combining what has been established by experimental observation with carefully recorded clinical data, there seems little reason to doubt the therapeutic value of the pancreatic extracts. Owing to their larger field of activity they are equally if not more valuable than the bile. But as we have already noted these actions are so bound together the one depending upon the presence or absence of the other it is a very difficult matter to say just where the chief importance rests. Naturally the one containing the largest amount of active ferment bodies must, in a sense, produce the largest result, and thus be of greatest importance. At the same time we must not lose sight of the value of these little catalysing bodies, how the absence of one may throw the whole digestive process out of balance; and until its loss is made good a perfectly normal state cannot be re-established.

After administering these extracts both alone and in combination for more than two decades, in all forms and types of indicanuria and disturbances of metabolism, the accumulated clinical experience and data obtained, certainly justifies beyond a question of doubt, the assertion that these extracts when properly made and carefully preserved do pass through the stomach without losing any of their digestive activity. That when they are brought into the natural place for their activity, they again resume their action and are of inestimable value as therapeutic agents. That without their aid it is almost an impossibility to manage these cases in the most successful manner.

In connection with the digestive function it is well to note that it not infrequently happens that the contents of the whole digestive canal becomes unduely acid and unless this condition is recognized and corrected by the administration of some suitable alkaline compound little or no improvement will follow regulation of the diet and digestive secretions.

We now come to the third factor to be considered or the nervous element. The state of the nervous system often plays a most important part, not only in exciting into existence, but in keeping in motion the indicanuria and its associated toxemia and disturbances in metabolism. In some rare instances the nervous mechanism may in a large measure be the direct predisposing cause, but more frequently it acts in a more decidedly secondary manner. Nevertheless, it must always be carefully considered in the study of every case. The only instances in which the nervous element can be considered as primary is when for some reason the nervous system has been subjected suddenly to some severe overstrain, one so great that it results in the action of the nervous system being very imperfectly performed. When this occurs the natural automatic balance of the system taken as a whole is decidedly interfered with and as a natural sequence the digestive function is very imperfectly performed as the result of the imperfect innervation. More frequently, however, the reverse is the case, the diet and digestion are primarily at fault in consequence of which the nutrition of the nervous system becomes impaired. Now, the imperfect stimulation and inhibition received by the digestive system through the nervous mechanism acts secondarily, yet it becomes a most

important factor to be considered in the analysis and treatment of every case. It must be carefully considered and corrected perfectly in the management of these cases if success is to be secured. The nervous system must be steadied, stimulated, and brought up from its deteriorated nutritive condition to one approaching the normal standard so that the automatic balance of the system may be re-established. Unless this is done no matter how well the diet, exercise, and hygienic conditions are adjusted, it is almost impossible to re-establish a perfect digestive state of the system. Once the nervous system has fallen into this condition, any slight overtaxation of the nervous mechanism will often act as the sole cause in producing profound exacerbations of the indicanuria, even though great care is being exercised continually as to the diet, exercise, and general hygienic conditions. This is especially noticeable in connection with great mental activity of the worrying kind, often witnessed among business men who are sorely pressed by the strenuousness of our modern times. This fact alone has misled many observers and caused them to look upon the nervous element as the primary and only condition to be treated, whereas the reverse is the true situation.

The more closely this great and complex problem is studied the more one is impressed with the necessity for studying each case separately and giving to each factor its true position and importance. Unless this is done treatment becomes of little avail.

With these varied indicanuric conditions, their associated toxemia, the impaired nutritive and functional activity of the nervous system, there are many instances in which the vascular tension becomes so much disturbed that it alone may be the essential factor that prevents recovery. It may result in too high or too low arterial tension. This being the case, both absorption from the alimentary canal and distribution of the nutritive pabulum throughout the system will be greatly disturbed; so much so, that this alone will be the cause of the impairment in the nutrition of all the structures of the body and especially so of the glandular system, heart, and nervous mechanism. The unduly high tension is the more damaging of the two conditions and has often been diagnosticated as an arteriosclerosis and very unfavorable prognosis given. While it is true that if the

condition is not correctly apprehended and treated it will eventually lead to a permanent lesion of the vascular walls. On the other hand, if the true condition is recognized and correctly treated both the indicanuria and toxic conditions can be overcome, after which, the vascular walls will return to their normal condition. This class of cases, however, is among the most difficult to manage and may take months and in some instances a year or two before the desired result is attained. The judicious administration of nitrite of soda in doses of two or three grains, in conjunction with the other remedial agents required, as a rule, yields the best results in the high tension cases. With the low tension the reverse line of action must be pursued. To this line of medication there must be added out of door exercise, which, however, is imperative in all cases and classes of indicanuria. But in this particular class it seems to be even more so than with any other from. Walking upon rough ground and moderate bicycling, are exceptionally good forms of exercises; the same may be said of golfing.

When all these foregoing conditions have been scientifically analyzed and practically treated we are then, and only then, in a strong position to consider what is the best method for inhibiting the action of the pathogenic bacteria, which is the essential factor in producing the putrefactive fermentation. The term inhibit is chosen because we cannot destroy the life of the germ without undue damage to the animal economy. Even if we could do so it would be unwise because we should destroy at the same time other microorganisms which are absolutely essential to a normal state of the digestive system.

It is just at this point, however, that the great error in the therapeutics of indicanuria is made, for almost every one seems to be looking for some one drug or combination of drugs that will at once destroy the action of the bacteria and thus arrest the putrefactive fermentation, thinking that by so doing the condition will at once be overcome and the system restored to a perfectly normal state. If we consider for a moment even, the three etiological factors already described and their bearing upon the action of the bacteria; and the very complex nature of the whole problem it seems incredible that any one should entertain for a moment so gross an error.

That we can in a measure inhibit the action of these pathogenic

microorganisms cannot be denied. This can be accomplished to a certain extent while we are dealing with the question of diet, defects in the digestive secretions and their actions, and the faulty action on the part of the nervous mechanism. The most phenomenal results, however, in the inhibition of the bacterial action, naturally follow the full correction of the predisposing conditions as already outlined. This is but natural for as we destroy the soil suitable to growth of the microorganism it ceases to be an active factor and easily yields to therapeutic measures.

Almost every antiseptic known to the *materia medica* has been lauded, from time to time, as a cure for indicanuria and all its associated complex conditions, and all have failed.

Large doses, or frequently repeated small doses of calomel will produce active catharsis and often sweep from the alimentary canal some of the bacteria together with the indoxyl potassium sulphate and the associated toxins. Under these circumstances the test for indican when applied to the urine will often give practically a negative result, and might lead one to believe that the condition had been removed. Such a result, however, has but little influence in the way of removing the pre-existing etiological factors just outlined, neither does it restore the system at large to a normal state. It unquestionably relieves the system for a few hours or days from the intensity of the toxemia, and by so doing enables the system to secure a better effect from other remedial agents. Very small doses of calomel, just sufficient to excite the hepatic cells to a little more perfect action, yet without cathartic effect yields far better and more lasting effects. This, however, is simply because it aids in making more perfect and more nearly normal the digestive secretions and thus augments their activity in reducing the foodstuffs to an absorbable condition.

Among the vast number of therapeutic measures that have been recommended and tried for the inhibition of the action of the pathogenic microorganisms in the alimentary tract, the three that have yielded the best results, in my experience, excluding the calomel as already outlined, are tannalbin, balsam copabia and asperin. The tannalbin acts largely by precipitating the thick, tenaceous mucus so abundant in the alimentary tract in connection with these cases and which acts largely as a cul-

ture medium for the pathogenic bacteria. Destroy the culture medium and the microorganisms will cease to thrive.

Just what the action of the balsam and the asperin is, remains an undetermined quantity, but a vast amount of accumulated clinical experience points strongly in their favor as against all the others that the author has used during the past two decades. The balsam and asperin are given in from two to five grain doses, usually in combination, or they may be added to the combination of *fel bovis inspissatum* and pancreatic extract. It should be remembered, however, as already noted that these here mentioned, are not and never can be specifics for this exceedingly complex and often very much complicated chemico physiological condition of the animal economy. Nevertheless, it is my firm conviction that when every factor in connection with indicanuria, its associated toxemia and disturbances in metabolism are correctly apprehended and scientifically treated in the order of their importance; that is assuming that the patients will do exactly what they are instructed to do, every case can be brought to a successful termination. The result may seem like one produced by a specific yet in no sense is it such. As already stated, however, it is no easy task that confronts us, but one that calls for consummate skill in every department of our medical science.

Until the profession as a whole grasp the extreme gravity and recognize the frequency of indicanuria and learn how to interpret correctly its true import there can be but little progress in its successful management. Until this is accomplished, in my humble judgment there will be comparatively little progress in medicine for it is only along the line of chemico pathology that true advance can be made. Just as soon, however, as the magnitude of the problem is fully apprehended and intelligently and diligently investigated there will be unquestionably great advances made in the prevention of the more chronic and incurable pathological conditions. Both the acute and chronic diseases will be less frequent. The health and happiness of the human race will be greatly augmented. Longevity will be still further extended and mortality progressively lowered.

