PENTOSURIA, CHRONIC AND ALIMENTARY.[1]

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IN view of its scientific interest, and its importance in connection with medical examinations for life insurance, the subject of pentosuria deserves a great deal more attention than has been accorded to it in this country. Of the score or so of cases found in the literature, considerably more than half have been recorded by some half-dozen observers in Germany. And while it may possibly be a condition which, like diabetes, is more common in Germany than here, yet it is more probable that in this country cases of pentosuria have been allowed to pass unrecognised. It is therefore of importance that publicity should be given to such cases as *are* recognised.

But, first, what is pentose? Pentose is a monosaccharid with five atoms of carbon and the formula $C_5H_{10}O_5$. It does not occur free in nature, but its anhydride pentosane is found in fruits, especially cherries, apples, pears, and plums; in corn and, to some extent, in all vegetables.

There are three main forms of pentose—arabinose, xylose, and rhamnose—whose properties are briefly as follows. Arabinose occurs in various forms—dextro-rotatory, lævo-rotatory, and optically inactive. It gives positive reactions to the following tests for sugar—Trommer's, Fehling's, Moore's, Nylander's, and the phenylhydrazin test. It does not ferment with yeast. Xylose and rhamnose are less optically active, but otherwise are almost identical with arabinose in their reactions.

Pentose may be recognised roughly by two tests—Tollens's test and the orcin-hydrochloric acid test. Tollens's test is carried out as follows. Three c.c. of urine are mixed with an equal quantity of fuming HCl in a test tube, and a few grains of pure phloroglucin added. The tube is then placed in boiling water. If pentose is present, a cherry red colour at once appears, followed by a black precipitate. This precipitate is now filtered off and dissolved in alcohol, forming a purplish solution, which, when examined with the spectroscope, shows an absorption band in the yellow and green part of the spectrum between the D and E lines of Frauenhofer.

The orcin-HCl test is practically the same in its technique. Orcin is used instead of phloroglucin; the colour is a bluish-green, not a red; and the band in the spectrum is between the C and D lines of Frauenhofer.

The only fallacy in connection with these tests is due to the possible presence of glycuronic acid in the urine, but this may be

[1] From the laboratory of Professor von Jaksch at Prague.

eliminated by finding whether the patient has taken any drugs which would produce a paired glycuronic acid in the urine. Such paired acid gives a positive reaction in Tollens's test, but not to the orcin test. It is still a question whether the unpaired acid ever appears in the urine or not.

It must also be noted that if pentose be present only in small quantity in the urine, the reduction tests for sugar are often delayed—the yellow oxide appearing perhaps only after the tube has cooled for some time.

Glancing now very briefly at the reported cases of chronic pentosuria, we find that the first case is that of Salkowski and Jastrowitz in Berlin in 1892. This was the case of a man, æt. 29, a morphomaniac and neurasthenic. He had a glycosuria due to morphia, but when he stopped taking this drug his urine continued to give marked reactions to Trommer's, Moore's, and Nylander's tests. An investigation was thereupon made, resulting in the demonstration of pentose—the first time that this sugar had been found in the animal kingdom.

The next two cases are described by Blumenthal. One was a man, æt. 36, always healthy, who was refused by an insurance office as being a diabetic. His urine markedly reduced copper and bismuth salts, but did not ferment. Ultimately the sugar was found to be pentose, not glucose.

The other was a man, æt. 65, considered to be suffering from glycosuria due to nervous disease. In this case there was marked history of nervous disease and diabetes in the family.

The fourth and fifth cases are recorded by Bial. The former was a Polish man, æt. 57, who was considered to have chronic diabetes, small quantities of sugar being constantly found in his urine. He was very emaciated, but otherwise healthy. The urine reduced copper and bismuth salts, but did not ferment. The reducing substance was found to be pentose. The latter was a man of 28, who had no symptoms of illness.

The sixth case is recorded by Fritz Meyer—that of a man æt. 39, with a neurotic family history. He was very pale and thin, and had always been so. He had applied for life insurance, and to his surprise and horror had been rejected as a diabetic. This diagnosis was made upon the grounds of a very strong reaction in Trommer's and Moore's tests—so strong that further tests were considered unnecessary. He consulted his doctor, who, finding that the urine did not ferment, examined for and found pentose.

The seventh case is that of an American woman, who for years had been considered an obstinate case of chronic diabetes, and had been subjected to various Carlsbad and other cures. In her case the urine was found to contain 1 per cent. of pentose, and no glucose.

The eighth, described by Brat, is that of a German woman,

æt. 62. Eight years previously she had become ill, and sugar being found in her urine, had been declared a diabetic. She had been for some time on diabetic diet, etc., without benefit, when the sugar was found to be pentose. Thereafter she recovered rapidly, her mind being freed from the fear of diabetes.

The ninth case is that of a brother of this lady, æt. 50, and quite healthy.

The tenth case is recorded by Colombini. It is that of a 50-years old Italian peasant, who came to the skin clinique at Siena with what appeared to be a xanthoma diabeticorum. His habitual diet was almost entirely vegetarian. His urine gave delayed positive results to Fehling's and Nylander's tests, but did not ferment. Pentose was ultimately found to be present. Under treatment, his skin trouble disappeared, and four months later investigation failed to show any pentose in the urine. This case is probably more an alimentary than a purely chronic pentosuria, as the "cure" consisted of his vegetarian diet being changed into a mixed one with milk and flesh. Unfortunately, it is not stated how long the pentosuria continued after the change of diet.

The eleventh case is recorded by Reale. The patient was a morphomaniac, and four days after the intermission of morphia the pentose disappeared. This case also is more probably one of alimentary pentosuria, induced by morphinism.

Other cases are recorded by Caporelli, again in a morphinist, by Barszewski, by Bendix, and by Luzzatto, but I have been unable to obtain the records of them.

The latest recorded case is that of a man who was sent to Professor von Jaksch at Prague. He had been considered for some time to be a diabetic, although not suffering from any pronounced symptoms. The urine gave positive reactions to the copper tests for sugar, and to Nylander's test. It did not ferment with yeast, and was optically inactive. Pentose was found to be present, the urine giving positive reactions to Tollens's, the orcin-HCl, and other tests, and a pentosazone being formed—in this case not in stars, but in the rarer form of wavy threads. Minute investigations were made by Dr. Franz Erben, who showed that the pentose was inactive arabinose.

Several very interesting observations were made upon this case. The ingestion of large quantities of glucose, lævulose, and lactose had no effect upon the quantity of pentose excreted in the urine. Further, the ingestion of arabinose was followed by an increase in the quantity of arabinose excreted, strictly in proportion to what had been given in the diet. Thus, in this case at least, none of these sugars was the source of the pentose which appeared in the urine.

The question now arises whether pentosuria is what might be termed a pentose-diabetes. A diabetes is characterised by an inability on the part of the body to consume all the carbo-

hydrates of the food. In pentosuria this does not occur. As has just been noted, quantities of glucose, lactose, and lævulose made no difference in the quantity of pentose in the urine in Erben's case. And these experiments have been made in other cases also with similar results. The administration of pentose itself, moreover, was followed by a strictly proportionate increase in the pentose in the urine. In a diabetes, any such administration of glucose would be followed by the excretion of an excess of glucose over the usual quantity, much greater than the quantity actually given in the food. For these reasons, therefore, pentosuria cannot be regarded as a pentose-diabetes.

It is more analogous to the condition of lævulosuria, where there appears to be some anomalous formation of lævulose in the organism, although the capacity to deal with the lævulose of the food remains unaltered.

Pentosuria has been called an anomaly of assimilation, for the reason that no explanation of it can be offered. There is no reason from the clinical data at our command to fix suspicion on any one organ or function; and unfortunately, in the only autopsy made on a case, so far as I know, no detailed examination was made, owing to an accident. The question remains, What is the source of the pentose—the body, or the food?

Putting aside cases of alimentary pentosuria, in which, as the name implies, the food is clearly the source of the sugar, many arguments have been adduced to prove that in cases of chronic pentosuria also the pentose is derived from the food. Detailed chemical processes have been worked out to show how the usually optically active pentose of the vegetable kingdom can be changed into the optically inactive pentose of chronic pentosuria. Methods have been demonstrated by which glucose can be oxidised into pentose and glyconic acid; and it has been suggested that, in the pentosuric, this process stops at the stage of pentose, while in the normal person it goes on to the glyconic acid stage. It has also been shown that the dextro-rotatory galactose, which is a product of the digestion of lactose, may be changed into inactive arabinose. Against all these theories may be pitted the fact that pentosuria has been induced in *starving* dogs by extirpation of the pancreas.

In favour of the body as the source of pentose is the repeated demonstration of pentose in the nucleo-proteids of many of the organs of the body. But it has been shown that in the pentosuric there is no evidence of an unusual destruction of nucleo-proteid going on, inasmuch as in the urine the uric acid and phosphoric acid totals remain normal.

Owing to the paucity of cases recorded, and the somewhat disconcerting lack of symptoms in a number of these, it is impossible to draw up any array of symptoms of pentosuria. There are, however, one or two points common to several cases. There is, firstly, an hereditary neurotic taint. In connection with this it

is to be noted that, in the last few years, Bial has shown that pentosuria occurs as a "family" anomaly. The frequent association of a drug habit with this condition may be put down as merely a manifestation of the neurotic taint, although, in the case of morphia, there may be some causal connection. Of actual symptoms we find obstinate neuralgia, general asthenia, extreme thinness, and extreme pallor occurring in several cases. In no recorded case has there been any real polyuria or excessive thirst; and, as a rule, the specific gravity of the urine has not exceeded 1025.

Diagnosis.—The diagnosis is simple. Provided a urine contains a substance which reduces copper sulphate on heating, which does not ferment with yeast, and which gives Tollens's and the orcin-HCl tests, one is justified in declaring it to contain pentose. Further proof is to form from it an osazone with a melting-point about 160° C. If this condition of the urine is found to be constant, and independent of the nature and quantity of the carbohydrates in the food, one may declare the condition to be chronic pentosuria.

Prognosis.—In this connection we are hampered by inexperience. There would appear to be no increased liability for a pentosuric to become a diabetic. And pentosuria does not cause that increased liability to infectious and other diseases which is such a dreaded feature of diabetes.

Treatment. — Diabetic treatment is worse than useless. A moderately full diet, with milk and flesh and a limited quantity of carbohydrate, appears to be the best. A pure proteid diet only aggravates any neuralgic symptoms that may be present. So far, drug treatment has been of no avail. Opium, as will be shown below, actually increases the quantity of sugar in the urine.

Alimentary Pentosuria.—Since the discovery of the clinical entity known as "chronic pentosuria," many observers have noted the existence of an alimentary form of pentosuria. Just as in most persons the ingestion of an excessive quantity of carbohydrates, from which glucose can be formed, leads to an "alimentary" or "dietetic" glycosuria, so in most persons the ingestion of a large quantity of food capable of yielding pentose leads to an alimentary pentosuria.

Pentosanes, the anhydrides of pentose, and bearing to it the same relationship as glycogen to glucose, are, as has been said, present in considerable quantity in fruits and vegetables. Pentose itself is present in almost all beers and in prepared fruit juice beverages.

Alimentary pentosuria has been found most frequently in summer, when large quantities of fruit and vegetables are consumed, and large quantities of beer and prepared "non-alcoholic" fruit juices drunk. This was first pointed out by Professor von Jaksch. He showed that, in either healthy or ill subjects, the drinking even of as little as 1 to 1½ litres of such fruit juice was

followed by the appearance of pentose in the urine. The urine in such cases gave distinctly positive reactions to Trommer's and Nylander's and Tollens's tests. On the other hand, it did not ferment. Such pentosuria, he observed, persisted for at least twenty-four hours.

Kaliski also reports having met with a man with pentosuria, due to his having eaten a good deal of fruit and drunk much beer. The urine gave a strong reaction to the reduction tests.

It was in continuation of the interesting observations of Professor von Jaksch, and at his suggestion, that the following experiments were carried out.

The aims of the experiments were to discover—(1) If it was possible to induce this alimentary pentosuria in everyone, or if some persons were endowed with the power of resisting it; (2) what was the minimal quantity of fruit juice necessary to produce pentosuria; (3) when pentose first made its appearance in the urine after the ingestion of the juice; (4) how long such pentosuria lasted; (5) whether the secretion of pentose produced any effect upon the total excretion of nitrogen in the urine; and (6) whether the administration of morphia had any effect upon this pentosuria.

Beer was obviously unsuitable for being given in large quantity to hospital patients; so also were raw fruits. Non-alcoholic prepared fruit juice was therefore chosen; and as "apple juice" was found to be the most popular, it was used throughout in these experiments. The exact brand was "Ceres Gesundheit's Apfelsaft."

A number of the patients selected were "nervous" cases in whom the alimentary and urinary systems were quite normal. Several cases were employed in which there was derangement of the liver. No renal cases were taken; but as there is no reason to believe that pentosuria depends to any extent upon the condition of the kidneys, this omission is not of any real importance. Unfortunately, no known case of pancreatic disease was in the clinic at the time.

The method of procedure was simply to give the patients selected a certain quantity of apple juice to drink after examination of the urine. The urine subsequently passed was then examined for pentose. Twenty-five sets of observations in all were made upon eighteen different patients. The following were briefly the conclusions reached in regard to the points enumerated above:—

1. *Can alimentary pentosuria be induced in every individual?*—Only two patients—11 per cent.—showed absolutely no trace of pentose in the urine after drinking 1½ litres of apple juice. Of these, moreover, one showed pentosuria on a second trial being made some time later with the same quantity of juice. The other case was a mild phosphorus poisoning, in which the liver was not much

affected. He left hospital before any observations could be repeated. Case 9 is uncertain.

In this connection two extraordinary results must be noted. One patient (Case 14) drank 1½ litres of apple juice daily for nine consecutive days. On the first and second days after the first dose of juice, the urine reduced copper and bismuth salts, but gave only indefinite reactions to the specific tests for pentose. An osazone was not obtained. Thereafter the urine ceased to show any abnormal constituent for five days, when it again reduced copper and bismuth salts, but gave positive results to no other test for any form of sugar or glycuronic acid—being unfermentable, optically inactive, and not forming an osazone. The only abnormality found after careful investigation was the presence of indican.

Another patient (Case 23) drank 1 litre of juice daily for six days. On the first day after she started, the urine contained pentose very definitely. But after that for ten days no trace of pentose or any other reducing substance could be discovered.

It would require further experiments to determine whether or not these patients developed an "immunity" or "tolerance" to pentose. It is conceivable that the first dose of pentose took the body, as it were, unawares; but that afterwards it was enabled to readjust itself to the altered requirements, and to bring into action an increased "combustion capacity" for pentoses, so that they no longer appeared in the urine.

2. *The minimal quantity of juice required to produce pentosuria.*—With regard to this point it was found that in normal circumstances ¼ litre did not produce pentosuria, whereas ½ litre did so in quite a number of cases. So that ½ litre may be taken as about the smallest quantity of juice that is followed by pentosuria. It is very interesting, however, that in two cases ¼ litre did produce pentosuria. One of these cases was a patient (Case 18) who was kept constantly under the influence of morphia. The other case (Case 24) was a tuberculous case; and in her ¼ litre produced pentosuria only when the administration of apple juice was accompanied by a hypodermic injection of 0·01 grm. morphine.

3. *The interval between the drinking of the juice and the appearance of the pentose in the urine.*—In seventeen cases pentose appeared in the urine within twenty-four hours. In a number of cases more exact times were calculated. The smallest interval noted was three hours, in Case 21, in which ½ litre of juice was given along with morphia. The interval was four hours in Cases 12, 18, 19, and 25. In 12, 3 litres were drunk. In 18 and 19 the patient was constantly under the effects of morphia. In 25 the administration of the apple juice was accompanied by an injection of 0·01 grm. morphia. In other cases the intervals varied from six, nine, twelve, sixteen, eighteen, and twenty to twenty-four hours.

4. *The duration of the pentosuria.*—This must be taken in connection with the quantity of pentosane ingested, as, with the exception of the two cases (14 and 24) already mentioned, the larger the quantity taken the longer did the pentosuria last.

In the two cases where with morphia ¼ litre was effective, the pentosuria lasted twelve hours in the one case, in which only a single injection of morphine was given, and twenty-four hours in the other, where the patient was always kept under the influence of the drug. Where ½ litre was given, the pentosuria lasted from twenty-four to forty-eight hours in different cases.

Where 1½ litres were taken, it lasted for three or four days; in one case for five days.

Where 3 litres were taken, it lasted in two cases for five and six days respectively.

5. *Effect of pentosuria upon the total nitrogen excretion.*—On this point my experiments show no definite conclusion. The nitrogen totals varied, according to the nature of the disease and diet, from about 4·5 to 22 grms., as estimated by Kjeldahl's method. In fifteen cases the total nitrogen excretion was estimated daily for varying periods, during which the patient was taking fruit juice. And whereas in eight the charts seem to point to a diminution of the total nitrogen excretion during the pentosuria period, in the other seven neither increase nor diminution can be observed. More experiments and of longer duration would require to be made before any decision on this question can be reached.

As far as they go, however, these results quite tally with those of von Jaksch after administration of xylose to both healthy and diabetic patients. With non-diabetic patients he found the results uncertain, although with diabetics there was an increase of the nitrogen excretion, showing that these sugars cannot be turned to good account by the diabetic.

6. *The effect of morphia upon alimentary pentosuria.*—The most interesting result of these experiments is, without doubt, the demonstration of the fact that the presence of morphia in the body diminishes its capacity to consume pentoses, so that they are more readily excreted in the urine.

In Case 19, a patient with sarcoma of the pelvis, who was kept constantly under the influence of morphia, a very distinct pentosuria followed the taking of ¼ litre of apple juice—a quantity which, as stated above, produced no effect upon a person not taking morphia.

In Case 22—a tabes dorsalis also kept under morphia—½ litre produced a much more marked pentosuria than was the case with normal individuals.

In Case 20, ½ litre of apple juice alone produced very little effect, while, when it was given along with an injection of 0·01 grm. morphine, a very distinct pentosuria resulted.

A final demonstration is afforded by Case 24, a tuberculous

patient, in whom the urinary and alimentary systems were absolutely normal. In her the drinking of ¼ litre of apple juice was followed by no trace of pentose in the urine. But two days later (Case 25) ¼ litre accompanied by an injection of 0·01 grm. morphine produced a distinct pentosuria; and a pentosazone was easily formed from the urine passed from seven to eleven hours after taking the juice.

The interest of this point is that it enables us to understand why pentose is so frequently found in the urine of morphomaniacs. Undoubtedly the morphomaniac must be less able than an ordinary individual to deal with and "burn up" the pentoses taken in with his food. There is no need, therefore, in such cases to search for the source of the pentoses in the body. They are derived from the food.

Of course this does not apply to such cases as the first case described by Salkowski. That case was clearly one of chronic pentosuria occurring independently of the morphinism, as it persisted long after the morphia habit had been given up. But it seems to me to explain such a case as Reale's, where the pentose disappeared four days after the morphia had been stopped. Such a case I should explain as being one of alimentary pentosuria partially induced by the morphia.

Is it not possible, however, that even in a case like that of Salkowski and Jastrowitz the chronic pentosuria was caused by the morphine habit, a long period of induced inability to completely utilise and dispose of the pentoses in the food leading ultimately to an organic inability to do so?

Conclusion.—Considering now the whole question of the chronic and alimentary forms of pentosuria together, it must be admitted that it is a question not only of great theoretical interest, but of great importance to the practical physician. A perusal of the cases recorded in the literature cannot fail to impress one with the fact that this condition may be very easily mistaken for diabetes mellitus. Nor is this mistake a slight one, as a diagnosis of diabetes by a physician is quite calculated to frighten most patients into a more or less morbid condition, even although they may have no symptoms.

It is well known that several substances besides glucose reduce copper salts on heating. But, at the same time, positive reactions to Trommer's test, especially if confirmed by positive reactions to Moore's and Nylander's tests, would be very apt to lead one to make at least a provisional diagnosis of diabetes. Nor is the polariscope a sure test. Dextro-rotation may be due to dextro-rotatory arabinose secreted in the course of an alimentary, not a chronic, pentosuria. And the phenylhydrazin test, as usually performed, is not calculated to show pentosazones, which have to be carefully formed, and carefully looked for in many cases.

It must therefore be emphasised that the fermentation test for grape sugar is the only one quite free from fallacy.

Professor von Jaksch recommends that, if one meets with a urine which reduces Trommer's and Nylander's solutions, one should perform a fermentation test, and either a Tollens's or the orcin-HCl test for pentose. At the same time it is well to inquire whether the patient has eaten much fruit or vegetable food, or has drunk anything recently, which might produce a pentosuria. For it will be recalled that the experiments just described show that, if a man drink 3 litres of fruit juice—not a very excessive quantity in hot weather—his urine may, for *five or six days* even, continue to give quite a marked reduction of copper salts. If the fermentation test is negative while the Tollens's or orcin test is positive, then one is dealing with a pentosuria.

To all medical men who are called upon to examine patients with a view to life insurance, the diagnosis of pentosuria is a subject of special importance. Any confusion with diabetes is of necessity a very serious matter for the applicant, as it would probably lead to his rejection. Under such conditions, above all, in which the patient is seen only on the one occasion, the necessity of diagnosing either a chronic or an alimentary pentosuria from a diabetes, or even a glycosuria, must be emphasised. In such cases a fermentation test should always be made, provided there is a positive reaction to Trommer, either when first heated or after cooling.

What importance should attach to pentosuria in the mind of the examining physician, it is difficult to say. But there seems to be no reason why a higher premium should be paid by the pentosuric than by a patient with merely a trace of glycosuria.

This, of course, must be conditioned by the nature of the pentosuric's symptoms, if any.

It is of considerable importance in this connection, too, to distinguish clearly between a chronic and an alimentary pentosuria, as there is no reason why a person who happens to have a slight alimentary pentosuria should be considered other than a perfectly sound and safe life.

For the sake of brevity, full tabulated details of the observations upon the individual cases are not given. But the following synopsis contains all the important points:—

In Case 12, after 3 litres of apple juice, pentosuria was noted on one to five days inclusive. In Case 13, after 3 litres of apple juice, pentosuria was noted on two to seven days inclusive. In Cases 6 and 8, after 1½ litres of apple juice, pentosuria was noted on two to four days inclusive. In Cases 1, 3, and 15, after 1½ litres of apple juice, pentosuria was noted on two to five days inclusive. In Case 11, after 1½ litres of apple juice, pentosuria was noted on two to six days inclusive. In Cases 2 and 10, after

1½ litres of apple juice, pentosuria was noted on three to five days inclusive. In Case 4, after 1½ litres of apple juice, pentosuria was noted on three to six days inclusive. In Cases 5 and 7, after 1½ litres of apple juice, there was no pentosuria. In Case 9, after 1½ litres of apple juice, the reactions were doubtful, but pentose was probably present on the third and fourth days. Cases 14 and 23 are fully described in the text. In Case 16, after ½ litre of apple juice, pentosuria occurred after six hours, and persisted for at least eighteen hours. In case 17, after ½ litre, pentosuria appeared after twelve hours, and persisted for at least twenty-four hours. In Case 19 (same patient as 18), after ¼ litre of juice, pentosuria appeared in four hours, and persisted markedly for twenty-four hours. In Case 20, the drinking of ½ litre of juice was followed by slight pentosuria in sixteen hours, lasting for four hours. In Case 21, after ½ litre of juice and a hypodermic injection of 0·01 grm. morphine, pentosuria appeared in three hours, and lasted for twenty-four hours. In Case 22 (patient under morphia), after ½ litre of juice, pentosuria appeared in four hours, and remained for at least six hours. In Case 24, the drinking of ¼ litre of juice was followed by no pentosuria. In Case 25 (same patient as 24), the drinking of ¼ litre of juice, accompanied by a hypodermic injection of 0·01 grm. morphine, was followed by pentosuria in three hours, lasting at least eight hours.

THE USE OF THE DOUBLE-WEDGE SPLINT IN TREATMENT OF FRACTURES OF THE HUMERUS.

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TREATMENT of fractures of the humerus, though perhaps a somewhat trite and well-worn subject, is still one of great importance to patient and surgeon. To the patient, because of the amount of disablement which results from an ununited or badly united fracture of the arm; and to the surgeon, because it is generally acknowledged that these awkward complications are to be found with greater frequency after fractures of the humerus than of any other long bone.

That the methods of treatment in use are not altogether satisfactory is shown by their number and variety, by the different patterns of splints, pads, wedges, or moulded appliances advocated in text-books and by writers on the subject.

Probably no routine method is universally applicable. Every fracture has its own points of difficulty, and requires individual consideration and treatment. Some of the methods in common use appear to me to be wrong in principle, and none to be entirely satisfactory. Chief consideration of the more frequent varieties