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ON POISONS FORMED FROM FOOD, AND THEIR RELATION TO BILIOUSNESS AND DIARRHŒA.

BY T. LAUDER BRUNTON, M.D., F.R.S.

"WHAT is one man's meat is another man's poison" is a wise saying, embodying the observation of many generations, probably indeed of many centuries. It is only within the last few years that we have begun to discover the true relationship between food and poison, through a number of researches which have been made in the last ten years, and especially in the last five, on the production of poisonous alkaloids from various sorts of food by putrefaction or even by simple digestion. Every now and again we meet with cases of individual idiosyncrasy, in which particular foods produce quite exceptional symptoms. Thus I know a lady in whom a single strawberry causes the face to swell up until the eyes become almost closed. But in addition to these very exceptional cases, we meet with numbers of people—we might almost say classes of people—to whom certain kinds of food are more or less injurious. Milk and eggs are two of the most valuable foods we possess, and in cases of sickness where the patient is unable to take solid food, or in typhoid fever, where farinaceous foods, however easy of digestion, are, sometimes at least, injurious, milk and eggs are invaluable. Yet both milk and eggs appear to be more or less injurious to many healthy persons, and have the evil reputation of being bilious. If we enquire more precisely what is meant by this term we find that these foods are apt, when taken at all freely, to produce sensations of discomfort which are referred partly to the digestive and partly to the nervous system. Sometimes these sensations appear within one or two hours after taking the particular food which disagrees; at other times they may not appear until its use has been continued for several days. For example, one person, an hour after taking eggs or milk, feels an unpleasant taste in the mouth, general malaise, and a frontal headache. In others, after eggs have been taken for two or three days together, the appetite becomes impaired, the intellect appears less clear, the conjunctivæ slightly yellowish, headache may occur, and the discomfort may culminate in an attack of vomiting or diarrhœa, or both. The vomiting and diarrhœa are sometimes, though not always, preceded by constipation; and both eggs and milk, on account of their constipating quality, are popularly known as "binding."

In some sensitive persons eggs do not merely produce the symptoms of so-called biliousness, but act as violent poisons. A well-marked instance of this kind I have seen in a friend of my own, who was attacked with violent vomiting and purging whenever she happened to take even a very small quantity of egg. So sensitive was she, that on one occasion she was persuaded to eat a small portion of cake by the assurance that it contained no egg. Unfortunately the statement was incorrect, and even the small piece of cake produced the usual symptoms of poisoning by eggs in her. In such a case as this the effect of the food as a poison appears to depend on the individual who takes it. With certain articles of food, which occasionally produce poisonous effects, these effects may be due in some instances to the individual who takes them, but in others to changes in the articles of food themselves. Thus cucumbers and melons are apt to bring on diarrhœa, which may be due in some cases to a peculiar sensitiveness of the persons who eat them, but in other cases the disagreeable consequences may ensue from an accidental development of purgative principles in the fruits themselves. There appears to be a tendency to the formation of purgative substances in all plants belonging to the natural order Cucurbitaceæ, of which the cucumber and melon are members. In the colocynth and elaterium plants the purgative properties acquire a high development, and even the cultivated melons and cucumbers appear sometimes to show a tendency to reversion in the same direction, and to acquire purgative properties more or less strong. In the case of animal food we find that poisonous properties are apt to appear either from particular modes of cooking, or from commencing decomposition. Thus, meat which has been baked in a pie, without a hole in the crust by which to ventilate it, is more apt to disagree than the same meat boiled or roasted. Meat which has been kept until it has become high, or fish which has become tainted, is also very apt to produce symptoms of poisoning.

Till within the last few years we have been very much in the dark regarding the causes of the different phenomena just mentioned, viz : the tendency of milk and eggs to produce biliousness, or to be actually poisonous to certain persons, and of nitrogenous food such as meat, fish, or cheese to act as poisons when putrefaction has commenced, or of farinaceous food such as rye and maize to become poisonous when attacked by fungi. Even yet a great deal remains to be done before the subject is thoroughly cleared up, but so much has been done by recent researches that it may be useful to give their results shortly and to indicate the bearing of these results on the pathology of disease, and more especially on the pathology of biliousness and diarrhœa. The cardinal fact which results from all these researches is that albuminous, or perhaps to speak more correctly proteid, substances which are themselves foods may be split up so as to yield poisons. This decomposition is usually originated by various species of low organisms, and especially of bacilli, but it may be effected by the digestive ferments of the healthy body. The poisons formed by the decomposition of proteid bodies such as albumen, fibrine, and gelatine vary not only according to the particular body which is decomposed but to the particular organism or ferment which sets up decomposition, and according to the temperature at which it occurs and the length of time that it continues. Some of the products of the decomposition of proteid bodies are poisonous, others are innocuous. Amongst the poisonous bodies we find various degrees of activity, some being but slightly poisonous, while others are most virulent. When these poisonous products are separated from each other and isolated, they may remain unaltered and retain their properties for a length of time, but, when mixed together, they are apt to undergo further decomposition and become inert.

In order to make it easier to remember and understand these different changes, I may perhaps be allowed to use a very homely comparison between the food we eat and the utensils we employ at our meals. Albuminous food will ordinarily do us no harm, although a large quantity of it eaten at once may mechanically produce uncomfortable distension of the stomach. The glass tumbler or earthenware plate that we use in taking our food or drink are also safe to handle, and will do no harm unless they strike with exceptional violence against some part of the body. But this holds good for albumen and for our utensils only while they remain whole, though the nature of the wholeness is different in the two cases, being chemical in that of albumen and mechanical in that of the utensils. When the tumbler or plate is broken across, the sharp edges may render them liable to cut the fingers, but the pieces may be put together with cement and they again become useful as before. When the chemical molecules of which albumen is composed are broken up in the process of digestion into peptones, these molecular fragments become dangerous, and peptones, when injected directly into the jugular vein, act as powerful poisons, producing loss of coagulability of the blood, fall of blood pressure, and death. But in the healthy body the peptones, formed by the digestion of albuminous matters in the digestion, do not enter the general circulation. Like the broken plate they appear to be cemented again into the kind of albumen known as globuline, during their passage through the portal vein and the liver. But it is not when the tumbler is merely broken in half, or albumen simply decomposed into peptones, that the fractured products are most dangerous. It is when the tumbler is broken into splinters that the pieces are most likely to produce serious injury ; it is when albumen has been split up so as to yield organic alkaloids that the products of its decomposition are most poisonous. Amongst the broken glass we may find several pieces which have no sharp points and little, if any, sharp edge, so that they will be almost innocuous, while others may have a point and edge as sharp as a dagger, and capable not only of producing injury but of destroying life, and amongst these sharp pieces we may find some which are much more dangerous than others. In like manner amongst the products of decomposition of albumen we find some which are innocuous and others which are poisonous, and amongst the poisonous we find various degrees of virulency.

If we select from amongst the splinters of glass one with a sharp point and edge and lay it aside by itself, it may retain its dangerous qualities unimpaired for years; but if we leave it to be shaken about amongst the rest, and still more if we continue the very process of striking by which the splinter was at first formed, its point will be broken, its edges blunted, and it will become once more harmless. Similarly the poisonous products of albuminous decomposition when isolated may retain their properties unimpaired, but, if allowed to remain together, and still more if exposed to the continuous action of the putrefactive process by which they were at first formed, they undergo further change and again become innocuous. On this account the products of the decomposition of albuminous matters vary much in their poisonous properties according to the time during which decomposition has gone on. At first they are only slightly poisonous, later on they become intensely poisonous, but at a later stage still their poisonous qualities disappear, and they become more or less innocuous.

It is evident that the splinters of glass will vary according to the kind of glass, mode of striking it, and the force which we employ. If we break a large soda-water tumbler we will get longer, stronger, and more dangerous fragments than if we break a wine-glass, but the force which would splinter the wine-glass might simply crack the tumbler, and that which would split the tumbler into dangerous splinters might crush the wine-glass into harmless fragments. In the same way we find that the nature of the albuminous material influences the nature of the products of putrefaction. When putrefactive bacteria are sown on the flesh of mammals, the substance they produce is an exceedingly active poison, neurine, while they produce when sown upon fish another poison differing chemically from neurine although closely allied to it and resembling it also in physiological action. This poison, muscarine, is very interesting, inasmuch as it had only been obtained from a plant, the *Agaricus muscarius*, or fly-fungus, until it was discovered by Brieger to be a product of the decomposition of fish. Brieger has also found that the typhoid bacillus, when cultivated in peptone, forms no poison, but when cultivated in meat jelly or meat infusion it forms two poisons which he has not yet isolated completely. One of these causes salivation, diarrhœa and paralysis; the other causes violent and exhausting diarrhœa. The importance of an exact knowledge of the substances which are produced by the decomposition of various foods by the action of typhoid bacilli on them is obvious. The plan of treating typhoid fever by an exclusively milk diet has probably saved many lives, but our use of this plan is to a great extent empirical. We do not fully know why it is successful, and although we may suppose that it is because the milk is non-irritating and does not irritate the intestinal ulcers, that is probably only a part of the truth. For milk may, and sometimes does, form very hard clots, which may pass through a great part of the intestine undigested, and as we see in children may actually be voided in this condition. Farinaceous food on the other hand is chiefly digested by the saliva and pancreatic juice before it reaches the lower part of the small intestine, and even if it did pass over the ulcerated surface ought to do no harm by its mechanical action. Acting on this idea I have sometimes given starchy food in typhoid fever but in a few trials it seemed to cause a rise in temperature, and I therefore abandoned it. If the effect of food in typhoid fever is a purely mechanical one upon the ulcerated intestine, calf's-foot jelly ought to be well tolerated; but if the typhoid bacilli decompose gelatine so as to produce alkaloids having a violent purgative action, the jelly will be very injurious.

The temperature at which the putrefactive processes occur greatly influences the rapidity with which the albuminous substances split up, and the nature of the products which they yield. When the temperature is low decomposition occurs slowly, but does so quickly when it is high. It is probable that it may be much modified by other factors, such as the quantity of moisture in the albuminous substance itself, or in the atmosphere generally; and also by electrical atmospheric conditions, such as those which occur before or during a thunderstorm, for it is an old observation that meat as well as milk often becomes tainted during the electrical conditions which are popularly expressed by the term "thunder in the air." The difference between the products of decomposition in hot and cold weather is illustrated by the alkaloids obtained from decomposing maize in summer and winter. The alkaloid which it yields in winter has a narcotic and paralysing action; but when it decomposes during summer it yields, in addition to this alkaloid, another one which has a tetanising action somewhat like strychnine. As the putrefactive processes go on more quickly during summer albuminous substances become poisonous much sooner than in winter, and again lose their poisonous properties more quickly by the progress of decomposition. As putrefaction may go on to a certain extent after the introduction of food into the intestinal canal, and will probably from the higher temperature and greater moisture go on even more quickly than outside, it is evident that poisons may be formed from the part eaten, and produce dangerous symptoms, while no poison can be found in the remaining parts of the same food. This is perhaps of special importance in regard to milk when used as a food for infants. Milk may apparently be quite sweet at the time it is given, and yet it may be really "on the turn," as the term is. When swallowed by the infant it may rapidly become sour, and disagree, while a portion of the same milk, especially if kept cool, may appear to continue sweet for some hours afterwards. It is highly probable that not the least advantage possessed by milk drawn directly from the breast, over that given by a bottle, is that the former is free from bacteria with which the latter is apt to be contaminated. Both may appear to be equally sweet when administered to the child, but the organisms present in the baby's bottle will continue their action after the milk has been taken, and render it liable to produce vomiting and purging, which, as we shall presently see, are symptoms of poisoning by putrefactive alkaloids.

The risk of contamination is much greater when a bottle with a long tube is used, for the bacteria readily find a lodgment in it; and it is to be remembered that not only do the bacteria present in the milk at the time it is swallowed continue to decompose it in the stomach, but they continue to multiply, so that if even a few are present in the milk when it is taken they may within a short time multiply greatly, and produce extensive changes in the food if they find conditions favourable to their growth in the intestinal canal.

I have already mentioned that even the primary products of albuminous decomposition by digestive ferments such as peptones are poisonous. But Brieger has lately shown that pepsine will split up albuminous substances still further, so that by digesting fibrine with artificial gastric juice he has obtained an alkaloid to which he has given the name of peptotoxine.

The bitter taste which appears during the digestion of meat, or of milk artificially, is suggestive of the formation of some alkaloid, but I do not know whether Brieger has ascertained this bitterness to depend on the presence of an alkaloid or not. Of late years the use of digestive ferments, and of artificially-digested foods, has become so common that a study of the products of albuminous decomposition is becoming of extreme practical importance, for it is possible that digestive ferments, like other powerful agents, may be edged tools, and capable of doing harm as well as good.

When we consider how many conditions influence the nature of the products of albuminous decomposition we cannot be astonished to find that very different substances have been obtained by different experimenters. The chemical operations required to isolate the different products are so complicated and laborious that most experimenters have been satisfied with obtaining extractiform bodies, and have not attempted to crystallise them. But without obtaining them in a crystallised form one cannot be sure that they are pure, and the recent investigations of Brieger are therefore of great importance, because he has not only obtained several products of decomposition in a crystalline form, but has subjected them to organic analysis, and thus ascertained their chemical composition. The products of decomposition, or, as returning to the illustration we have already used, what we may term the splinters into which the albuminous molecule breaks up, are partly poisonous and partly innocuous. One fragment, as we may term it, which Brieger has got from flesh, is a substance called neuridine, which is innocuous, another, neurine, which is poisonous. From decomposing fish he has obtained a third substance, muscarine, which is more poisonous still, and two other substances, ethylenediamine, which is also poisonous, and gadinine, which is innocuous.

Besides the substances which Brieger has got from decomposing flesh, fish, and cheese, in which decomposition has been artificially induced, he has obtained from human corpses a different set of bodies, one of which he calls cadaverine, and the other putrescine, which are feeble poisons, and two others which are produced later and are more powerful poisons, causing paralysis and death.

In addition to the alkaloids obtained by Brieger, a number of poisons have been got by other workers from decomposing articles of food or from dead bodies, and even from portions of healthy animal bodies. Although these may perhaps not have been got in the same state of purity, nor have had their chemical constitution so well defined as Brieger's, they are still of great interest and importance. It is evident that when putrid substances are introduced into the body we must be careful to distinguish between the effects produced by the poisonous products of albuminous decomposition and those of the bacteria themselves, for the bacteria after their introduction may act upon the blood and tissues, and form poisons within the body itself even though none were present in the matter injected. Kerner appears to have been the first to suspect the formation of alkaloids by the decomposition of albumen, and in 1820 he pointed out the resemblance between the symptoms of poisoning by sausages and by atropine. He made experiments upon animals, and appears to have thought at first that an alkaloid was present in the poisonous sausage, but afterwards he forsook the idea and regarded the fatty acids as the poisonous agent.

The researches of Magendie and Gaspard on the effects of decomposing organic substances were important, but rather as affording a starting-point to researches on the effects of low organisms on the animal body than on the effect of chemical poisons produced in the putrefaction.

In 1856 Panum showed that the inflammatory change which occurs in the intestinal mucous membrane of animals poisoned by putrid matter is not due to the microbes contained in it, but to a chemical poison which remained unaltered when its aqueous solution was boiled for a long time. His conclusion that the poison contained in putrid matter was of a chemical nature was confirmed by C. O. Weber, Hemmer, Schweninger, Stich, and Thiersch.

Bergmann and Schmiedeberg isolated a crystalline poison from decomposing yeast, to which they gave the name of sepsine.

Bence Jones and Dupré found a substance resembling quinine in the liver.

Zuelzer and Sonnenschein obtained both from macerated dead bodies and from putrefied meat infusion small quantities of a crystalline substance which exhibited the reactions of an alkaloid and had a physiological action like atropine, dilating the pupil, paralysing the muscular fibres of the intestine, and increasing the rapidity of the pulse.

Rörsch and Fasbender obtained from dead bodies a substance which had properties like digitaline, but which was not crystalline.

(*To be continued.*)

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(*Continued from* p. 121.)

GAUTIER obtained from putrified proteid substances, and also from the secretions of living beings, alkaloidal bodies having a poisonous action. But the greatest impulse to the study of putrefactive poisons was given by Professor Selmi of Bologna, whose researches were unfortunately too soon brought to a close by his death. To alkaloids formed by the decomposition of proteid substances he gave the name of ptomaïnes, by which they are now known. It was at first supposed that these differed in their nature from organic alkaloids formed by vegetables, and various reactions were given to distinguish between them. Recent researches appear to show that this distinction can no longer be maintained, and that both animal and vegetable alkaloids are similar in their chemical constitution, and are both products of albuminous decomposition. I have already mentioned Brieger's discovery that an alkaloid peptotoxine is formed during the digestion of fibrine by artificial gastric juice. Pellicani has found a poison in the suprarenal capsule, and sometimes ptomaines may be obtained from the flesh of healthy animals. It is, therefore, probable that poisonous alkaloids are continually being formed in healthy men and animals by the decomposition of albumen in the intestinal canal during the process of digestion, or in the blood and tissues generally by the metabolism which occurs during the functional activity, A considerable portion of these alkaloids is in all probability destroyed in the body, but some are excreted in the urine and fæces, from both of which powerful poisons have been extracted.

It used to be an old saying that nature never provided a poison without providing an antidote, and the fact that the dock leaf and the nettle usually grow together is often pointed to as an illustration. In the case of poisonous alkaloids there seems to be a good deal of truth in this saying, for various poisonous alkaloids which have an antagonistic action to each other appear to be produced by albuminous decomposition. It has not yet been ascertained how far the symptoms of poisoning from decomposing fish, flesh, or sausages, or from the retention of morbid products of the organism itself, such as we see in cases of uræmia, depend upon a single poison or on a mixture of poisons. It seems, however, very probable, that in many such cases we have more poisons than one, and that the comparative absence of symptoms in some cases may be due to one poison counteracting another. Brieger has found that two of the most important alkaloids produced by putrefaction are neurine and muscarine; and to these may be added a third substance, choline. Choline is obtained by boiling bile, brain, or yolk of egg, with baryta, and gets its name of choline from its having first been obtained by treating bile in the way just mentioned. It has for some time back been considered to be identical with neurine, but Brieger has been led by his recent researches to regard choline and neurine as two different bodies, though very closely allied in their chemical constitution. By oxidising choline, obtained either from bile or from yolk of egg, with strong nitric acid, Schmiedeberg and Harnack have prepared artificial muscarine, which is almost, though perhaps not quite, identical with that which is found naturally in a poisonous mushroom (the *Amanita muscaria*). Recently Boehm has subjected choline and muscarine to a careful examination, and while he finds that their action is somewhat the same in kind, it varies in degree; muscarine being very much stronger than choline, and having a marked action on the heart of the frog which choline lacks. Artificial muscarine differs also to a certain extent from natural muscarine, inasmuch as the artificial alkaloid possesses a paralysing action on the ends of motor nerves, somewhat resembling that of curara, while the natural muscarine, if it possesses this action at all, has it only to a slight extent. With small doses the effects of artificial and natural muscarine are almost identical, and it is only when the dose is large that the paralysing action upon the motor nerves of the artificial muscarine becomes evident. It may be said that all three bodies—choline, neurine, and muscarine—have a similar action, but choline is much weaker than the other two. The lethal power of neurine is nearly ten times, and that of artificial muscarine fifty times, as great as that of choline. The most marked symptoms which they produce are salivation, diarrhœa and vomiting, dyspnœa, paralysis and death. They seem to stimulate the secretion of glandular organs, because along with salivation there is also a flow of tears, and the secretion of bronchial mucus is rendered abundant and fluid as is shown by the occurrence of abundant moist *râles* within the chest. The dyspnœa, however, is not entirely due to abundant secretion of bronchial mucus in the lungs, because even in frogs choline produces a peculiar alteration of the respiration and dyspnœic movements.

Muscarine and neurine produce in frogs a complete arrest of the cardiac pulsations, the heart stopping in diastole;[1] but this cannot be regarded as the cause of the dyspnœa, because the respiratory movements in frogs are not dependent on the circulation in the same way as they are in warm-blooded animals. In mammals[2] muscarine and neurine render the beats of the heart slow and weak, but do not usually arrest the cardiac pulsations, so that the heart is commonly found to be beating after death has occurred. The dyspnœa produced by muscarine has been attributed by Schmiedeberg to excitement of the respiratory centre in the medulla oblongata;[3] but I am inclined to think that in all probability contraction of the pulmonary vessels may have something to do with it; for one of the most marked points about the action of muscarine, neurine, and choline, is the extraordinary effect of atropine as an antidote to them. In animals poisoned by any of these three substances the subcutaneous injection of atropine stops the salivation, arrests the diarrhœa, and removes the dyspnœa. It also prevents death from these poisons, but only within certain limits: for if the dose be very great, the animals may still die. More especially is this the case with choline and artificial muscarine which

[1] Brieger, *Ueber Ptomaine*, pp. 26 and 34. [2] Brieger, *Op. cit.*, pp. 29 and 34.
[3] Schmiedeberg and Koppe, *Das Muscarin*, p. 50.

paralyse the ends of the motor nerves, because the curara-like action is not counteracted by atropine, but is perhaps rather increased, atropine itself having also the power of paralysing the motor nerves when given in large doses. The effect of muscarine and neurine on the heart is also removed by atropine. It is possible that atropine removes the dyspnœa by destroying the effect of these drugs upon the heart and thus allowing the circulation to go on freely again. Yet as I have mentioned in a former paper, the injection of muscarine causes the lungs to become pale, while the subsequent administration of atropine makes them regain their normal rosy colour, and I am inclined to attribute the dyspnœa produced by muscarine, partly at least, to contraction of the pulmonary vessels, and to regard the dilatation of these vessels by atropine as one of the reasons at least why this drug removes the dyspnœa.

Although, as I have already said, we do not as yet know that ptomaïnes having a physiological action like atropine, are generated in the intestines or in the tissues, at the same time as muscarine, neurine, or choline, it appears quite possible that such may be the case, and that we may have symptoms occurring which are due either to the mixture of two alkaloids or to the preponderance of one or other. A case of uræmia which I saw a few days ago was strongly suggestive of poisoning by a mixture of atropine and muscarine. The secretion of urine had completely stopped, the skin, eyes, and mouth were all dry, the pupil was somewhat dilated, the pulse was beating at the rate of about 130, the mouth was held constantly open, and the breathing was laboured and gasping, but air entered abundantly into the lungs, and there was no secretion of bronchial mucus. All these are symptoms such as we find from poisoning by atropine, but in two respects the symptoms resembled those produced by muscarine, for the skin was pale instead of being scarlet as in belladonna poisoning, and when cups were applied over the region of the kidneys in order to restore if possible the renal secretion, very little blood flowed from the incisions.

I have already mentioned that Zuelzer and Sonnenschein have obtained from putrefying meat infusion, a substance having the chemical reactions and physiological effects of atropine; and some such alkaloid appears to occur frequently in poisoning by sausages, so that in a case of sausage poisoning at Wildbad in 1793 the medical man who treated the case came to the conclusion that some one either through carelessness or design had put belladonna into the sausage.

In another case of sausage-poisoning described by Dr. Kaatzer, a family ate some smoked sausage at their mid-day meal; in half an hour afterwards they became unwell, with feelings of languor, fatigue, and drowsiness, yet with such dryness of the mouth that they were unable to sleep, and were obliged to be constantly drinking. In addition to this, the father had obstinate vomiting. Next day the dryness of the throat was so much greater they could hardly swallow, and the sight became affected. On the third day the symptoms were worse, the pupils were widely dilated, there was double vision, dryness of the mouth and of the nose, and when bread was chewed it was ejected again from the mouth as dry as when it was put in. Next day the child of twelve years old died with symptoms of œdema of the lung; and the father, though much affected, could not weep as his lacrimal secretion was paralysed. The father and mother gradually improved, but on the fourteenth day of the poisoning there was still complete paralysis of accommodation. In all of them, just as in the case of uræmia which I have just mentioned, there was paleness instead of redness of the face—a symptom which I am disposed to regard as possibly indicating the presence of a muscarine-like poison, in addition to one like atropine.

In other cases of sausage-poisoning additional symptoms have been noticed, which point to the existence of a muscarine-like poison also. These are the presence of diarrhœa, alternating with constipation, and of colic. The pulse also is sometimes slow, small, and almost imperceptible—a condition which is typically that of muscarine poisoning, while in atropine poisoning the pulse is rapid from the complete paralysis of the inhibitory fibres in the vagus which the poison produces.

It is possible that instead of there being two or more poisons having a partly antagonistic action there may be only one having an action resembling atropine in some respects and muscarine in others. In some cases of poisoning by fish the symptoms have been those of poisoning by atropine, viz., dryness of the mouth, difficulty in swallowing, weight of the limbs, paralysis of the superior and inferior recti and of the oblique muscles of the eyes, as well as ptosis and paralysis of accommodation, dilatation of the pupil and double vision. The pulse was, however, not quickened as it is in poisoning by pure atropine.[1] V. Anrep[2] states that he has isolated an alkaloid from poisonous fish, which produces similar symptoms to those just described as caused by fish itself, and Vaughan[3] has obtained from poisonous cheese an alkaloid which he calls tyrotoxicon which produces symptoms similar to those caused by cheese or by fish. If the alkaloid should turn out to be perfectly pure we should be obliged to regard them as having an action similar to atropine in many respects, but differing from it in respect to their action on the pulse. When we remember, however, how many vegetable alkaloids previously supposed to be pure have been recently shown to be mixed with others having a perfectly opposite action, we may still regard it as probable that the symptoms of poisoning by sausages, fish, &c., may in many cases be due to a mixture of alkaloids.

In cases of poisoning by a ptomaïne having a purely atropine-like action, the treatment indicated, which has also been adopted in at least one case, is the administration of physostigma either by application to the eye, or perhaps still better, by subcutaneous injection. In cases, however, where the symptoms are of a mixed character, our knowledge of the combined effects of the poisons is insufficient at present to enable us to decide with certainty whether medication of this sort would be useful or injurious in any given case, although we may try that alkaloid as a remedy which will tend to remove the most prominent or distressing symptoms. It is evident that if an atropine-like poison is present in the body at the same time with choline, neurine, or muscarine, in sufficient quantity to antagonise them the effects of those latter poisons will hardly be observed, although they may possibly evidence their presence by producing diarrhœa alternately with constipation. But if they are present alone, they may be expected to produce salivation,

[1] Schreiber, *Berlin. klin. Wochenschr.* 1884, xxi. pp. 162, 183.

[2] V. Anrep, *Vratch*, 1885, p. 213, abstracted in *London Med. Rec.*, 1885, p. 271.

[3] Vaughan, *Detroit Lancet*, August 1885, p. 60.

vomiting, purging, and collapse, according to the quantity which is taken into the system.

Where the symptoms are markedly those of a muscarine-like poison, we may try atropine as a remedy; and in one case lately it seemed to me to do good. A servant girl had taken at dinner some fried liver, and ten hours afterwards she was seized with vomiting and purging, which lasted the whole night. I saw her next morning and gave her some bismuth and soda, but the vomiting continuing I gave her fifteen drops of tincture of belladonna, and there was no vomiting afterwards. Of course this single case is quite insufficient to found a treatment upon, but I think that the administration of belladonna or atropine may be worth a trial in cases of poisoning by articles of food where the symptoms are those of muscarine or some allied poison.

Four alkaloids which Brieger has isolated from cadavers, viz., neuridine, cadaverine, putrescine, and saprine, have no marked physiological action; but he has isolated from human cadavers in an advanced stage of decomposition two alkaloids having a very powerful physiological action. One of these, when injected into guinea-pigs or rabbits, appeared to affect the intestine alone, and to have no action on any of the other organs. It caused an enormous increase in the peristaltic action, which lasted for several days, and the continuous diarrhœa led to extreme weakness of the animals.

Another alkaloid, which he terms mydaleïn, has a still more marked physiological action, and one which is of great clinical interest, inasmuch as we find amongst the symptoms a rise of temperature. No one who has watched cases of acute disease, such as pneumonia, can have failed to see how a rise of temperature sometimes coincides with the occurrence of constipation, and is removed by opening the bowels. In the case of such an acute disease as pneumonia, one has hitherto been unable to say definitely why constipation should produce this rise of temperature, but it seems not improbable that it may be due to the absorption from the intestine of some ptomaïne. In his work on *Purgative Medicines* also, Hamilton says that in cases of typhus fever the administration of an antimonial remedy "was beneficial only when it moved the belly. In this case the fæces were black and fœtid, and generally copious. On the discharge of these, the low delirium, tremor, floccitatio and subsultus tendinum which had prevailed were abated; the tongue, which had been dry and furred, became moist and cleaner; and a feeble creeping pulse acquired a firmer beat."

The action of mydaleïn is according to Brieger perfectly specific in its nature. When a very minute quantity of it is injected into guinea-pigs or rabbits the under-lip in a short time becomes moist, the nasal secretion becomes more abundant, and a copious secretion of tears occurs. The pupils then become dilated, the vessels of the ear become much injected and the rectal temperature rises from 1°—2° C. The pupils gradually dilate to the maximum and cease to react to light. The coat of the animals becomes staring and sometimes they tremble; gradually the secretion of saliva diminishes, the respiration and pulse, which at first were very rapid, become slower, the temperature falls, the ears become paler and the animals recover. During the action of the poison the animals show a tendency to sleep, and the peristaltic action of the intestine is increased. When larger doses are injected into guinea-pigs, even although they are still under half a centigramme ($\frac{3}{40}$ of a grain), their action is exceedingly violent and always fatal. The secretion of all organs composed of involuntary muscular fibre becomes exceedingly profuse; and the saliva becoming mixed with the intestinal discharges, the animals constantly lie in a puddle, especially as the power of motion is impaired; exophthalmus occurs and the dilated pupils are difficult to examine on account of the profuse lacrimal secretion. When the action of the poison has attained its maximum the animals fall down, first the hind legs and then the fore legs becoming paralysed; fibrillary twitchings are visible in various groups of muscles, and the respiration becomes more and more violent and gasping. Sometimes the animal makes a sudden upward spring, raising its head and gasping for air; then it sinks down again and lies in its excrement, making slight defensive movements with its legs. The temperature gradually sinks, the movements become slighter and slighter, and finally the animal dies. On post-mortem examination the heart is found standing still in diastole and the bladder and intestine are contracted, but there is nothing else abnormal. In cats mydaleïn caused dilatation of the pupil; profuse secretion of tears, saliva, and sweat, vomiting and diarrhœa: to these succeeded paralysis first affecting the hind-legs and then the fore-legs occasionally convulsive twitchings, laboured breathing, coma and death. On post-mortem examination the heart was found standing still in diastole, the intestines contained a little thin fluid secretion, and the mucous membrane was injected. This alkaloid is, as I have already said, very interesting from the rise of temperature which it produces; but we do not as a rule find all the symptoms here described as characteristic of poisoning in animals occurring usually in men, either in cases of disease or in consequence of poisoning by decomposing food, although a number of them may occur. It is possible that the occurrence of some and not of others may be due to the occurrence in disease of alkaloids allied to mydaleïn, although not identical with it; or to the presence of two or more alkaloids which partially neutralise each other's effects.

(*To be continued.*)

ON POISONS FORMED FROM FOOD, AND THEIR RELATION TO BILIOUSNESS AND DIARRHŒA.

BY T. LAUDER BRUNTON, M.D., F.R.S.

(*Continued from* p. 200.)

It is quite evident that it would be unjustifiable to conclude that because alkaloids are formed by the decomposition set up by bacteria in albuminous matters outside the body, they are therefore formed constantly within the body, either in health or disease, however probable such a conclusion might be. But positive evidence that such a formation of alkaloids does occur in the intestine is afforded by the fact that alkaloids are found in the freshly voided fæces.

That alkaloids are present in the circulating blood, is shown by the fact that they are separated from it by the kidneys, and are found in the urine. The effect of ptomaïnes formed in the body in producing disease has been investigated by Bouchard, who has found that the poisonous activity of human fæces is very great, even when they are quite healthy, and a substance obtained from them by dialysis produces violent convulsions in rabbits. Bouchard considers that the alkaloids formed in the intestine of a healthy man in twenty-four hours would be quite sufficient to kill him if they were all absorbed and excretion stopped. When the functions of the kidneys are impaired, so that excretion is stopped, uræmia occurs: and to this condition Bouchard would give the name of stercoræmia, because he thinks it due to alkaloids absorbed from the intestines. The nervous disturbances which occur in cases of dyspepsia, and of dilatation of the stomach, he thinks are due to nothing else than poisoning by ptomaïnes. Lépine and Mollière describe the case of a man suffering from intestinal constriction, who suddenly became ill and died in two days with all the symptoms of atropine poisoning, redness of the skin, delirium, dryness of the throat, extreme dilatation of the pupils with loss of reaction to light and rise of temperature. There was nothing to show that the patient had taken atropine or belladonna, and Lépine and Mollière consider that he died from ptomaïnes formed in the bowel and absorbed from it. They found in the contracted intestine a fæcal mass having a particularly bad smell, and they think that it was the source of the poisoning.[1] There seems to be little doubt that the amount of ptomaïnes formed in the body in disease is greater than it is in health; and very probably they are of a different character, possibly varying with the disease. According to Lépine and Guérin the poisons contained in the urine in different diseases differ in their physiological action. The extract obtained from the urine in cases of typhoid produced in frogs increased reflex action and death after three hours, the heart being usually found in a state of diastole. In cases of pneumonia the urine had a similar action, except that the heart was found in a more or less contracted state, varying with the severity of the case from which the urine had been obtained. One author has gone so far as to consider that the immunity which one attack of an infective disease confers against a subsequent one, is due to alteration in the body, not by bacteria, or other low organisms, but by a chemical substance which they produce; and he has proposed to afford protection against the disease by cultivating the bacteria artificially and inoculating with the poison which they produce without the bacteria themselves. This does not seem a very promising method of treatment, but we are likely to obtain most useful information regarding the proper diet in disease, and especially in cases of intestinal disease, by observations on the nature of the poisons which bacteria produce when cultivated in different kinds of food.

This investigation has been begun by Breiger, who found that the typhoid bacillus, although it grew well in peptone, appeared to form no alkaloids from it—at least he was unable to obtain any. When he cultivated it in beef-tea, however, he obtained as a product of decomposition an exceedingly small quantity of ptomaïne, which had a marked peculiarity in its action, namely, that after death from it the heart was found

[1] Lyon Méd., No. 42, 1884. [2] Lyon Méd., No. 24, 1884.

constantly in a state of systolic contraction, whereas most of the other alkaloids obtained from putrefying substances, such as muscarine, tend to produce stoppage of the heart in diastole. This alkaloid when given to guinea-pigs caused slight salivation and increased rapidity of respiration; later on the animals lost control of the muscles of the extremities and trunk, although there was no definite paralysis of the muscles themselves. The pupils became dilated and no longer reacted to light, salivation was profuse, and there was constant diarrhœa; the respiration and pulse became slower, but sometimes the animals did not die until after twenty-four or forty-eight hours. On *post-mortem* examination, in addition to the systolic contraction of the heart already mentioned, hyperæmia of the lungs was found, but the other organs were pale. The intestines were firmly contracted, and their walls were pale. Most of the alkaloids which have been obtained by the decomposition of albumen appear to belong to the muscarine type, and to have a tendency to cause diarrhœa, although some appear to belong rather to the atropine type, which, to a certain extent, counteracts the effects of muscarine.

No alkaloid having a well characterised chemical formula appears as yet to have been isolated from cholera stools, but Nicati and Rietsch [1] have produced choleraic symptoms in animals by cultivations of the comma bacillus from which the bacilli themselves had been removed; and somewhat similar results were obtained several years ago by Lewis and Douglas Cunningham with cholera stools in which any organisms present had been destroyed by boiling. In view of the extraordinary activity of some of those alkaloids, we cannot wonder at the violent symptoms which sometimes occur after the use of tainted meat, nor even at the extraordinary poisonous action of eggs in some persons. It is probable that the diarrhœa and vomiting which are produced by tainted meat, are due to the poison formed from the albuminous substance of the meat, by low organisms, either before it has been consumed, or by decomposition in the intestinal canal itself. In most persons eggs are harmless, but the yolk of eggs contains, in considerable quantity, lecithin from which choline may be readily formed; and if we suppose that

[1] *Compt. rend.*, xc. 928.

in certain individuals choline, or perhaps even muscarine, is formed from eggs during digestion, we can readily see why this useful article of diet should prove to such persons a violent poison. It is more difficult to say why milk should, in some persons, prove poisonous. Milk also contains lecithin, but in small quantity; and all we can say about it at present is that, in some individuals, a poison is probably formed from it, which causes it to disagree.

But even when milk and eggs do not cause any immediate disturbance of the digestive functions, they sometimes produce, when taken for several days together, a condition which is generally termed biliousness. It is rather hard to define this condition, inasmuch as the term is an elastic one and includes a number of symptoms. Amongst them may be said to be a tendency to eructation and acidity with an appetite which sometimes is very good, sometimes is bad, and sometimes is capricious. These symptoms may depend upon the condition of the stomach itself, but they may also be due to derangement of the liver, for all the venous blood from the stomach must pass through the liver on its way to the general circulation, and any obstruction to the hepatic circulation will produce venous congestion of the stomach and consequent disturbance of its functions. But these symptoms are not unfrequently accompanied, or succeeded after an interval of a day or two, by others which point more distinctly to the liver itself, such as slight frontal headache, a sallowness of complexion, a faint yellowish tinge of the conjunctiva, and a bitter taste in the mouth. These are usually attributed to the presence of biliary matters in the blood, the colour of the face and conjunctiva being attributed to bile pigment, and the bitter taste in the mouth to bile acids. But bile acids are not so very bitter—they are rather bitter-sweet, and healthy bile has no bitter taste, so that it seems that the bitterness in the mouth may, with more probability, be attributed to some alkaloid circulating in the blood, and excreted by the salivary glands. Along with this condition we sometimes find that the stools are pale, and then the explanation of the symptoms is easy, for we at once conclude that there is a catarrhal condition of the stomach and duodenum, and that the swollen mucous membrane presents a mechanical obstacle to the flow of bile from the liver. The pressure of bile in the biliary passages is thus increased, and absorption occurs. This explanation seems so satisfactory that we hardly care to look for another. But it is quite possible that it is not the true one. The real cause may be that the bile has become so viscid that it will not flow through the ducts, and even when the tendency to secrete such thick bile has passed away, the viscid bile already formed may plug the ducts and cause the jaundice to continue, even though the mucous membrane of the ducts and duodenum should be healthy. Moreover, we sometimes find that instead of the stools being paler than usual they are darker than usual, and it seems rather hard to say why we should have more bile than usual passing out into the intestine, and at the same time have bile absorbed into the blood. But here we gain much information from observations on the action of poisons. Schmiedeberg noticed that toluylendiamine, a substance belonging to the aromatic series, produced jaundice; and the action of this substance has been further investigated by Stadelmann. Their observations show that this poison causes increased destruction of blood corpuscles in the liver, with increased formation of bile. At first all the constituents of the bile, both the solids and the water, are increased, so that a greater quantity of bile is secreted; but as the action of the poison goes on the solids are excreted in greater quantity than the water: and so along with a great increase in the biliary solids secreted, the bile itself becomes more and more viscid, until at length it will not flow through the bile ducts, and thus absorption and jaundice takes place—although there is no mechanical obstacle to the passage of the bile into the duodenum. The first stage of the action of this poison corresponds to the condition of biliousness with excess of bile in the stools. It is possible that the second stage may correspond to so-called catarrhal jaundice, especially in epidemics, though it is also possible that the usual explanation of the causation of catarrhal jaundice may be in many cases the correct one.

It is probable that other bodies belonging to the aromatic series have also a considerable action on the biliary secretion, for salicylate of sodium is a powerful hepatic stimulant, greatly increasing the secretion of bile. Unlike toluylendiamine, however, it greatly increases the water of the bile, and renders it thinner instead of more viscid. We do not as yet know what the action of the aromatic compounds formed in the intestine is upon the secretion of bile, but we know that a number of aromatic compounds are formed in the body and are excreted in the urine. These bodies are formed both in health and disease, and carbolic acid occurs in the urine of healthy men. It becomes much increased when the peristaltic movements of the intestine are interfered with;[1] and occurs also in much larger quantity than normally in some cases of infective disease, such as diphtheria, facial erysipelas, pyæmia, and scarlet fever.[2] So far as I know toluylendiamine has not been obtained as a product of albuminous decomposition; but another substance having, like it, the power of producing intense jaundice has been got from lupin seeds. Sheep fed upon these seeds frequently die, and one of the most marked symptoms is intense jaundice. From these seeds Kühn[3] extracted a substance to which he gave the name of ictogen; and this substance has been further purified by Arnold and Schneidemühl, who give it the name of lupintoxin. It does not appear to be an alkaloid, but rather a substance of an acid nature, but what its exact chemical nature is has, so far as I know, not been exactly ascertained.

Along with biliousness we frequently find headache, and many severe headaches associated with vomiting are popularly known as bilious headaches. Modern pathology is inclined to regard the so-called bilious headaches as rather of nervous than of hepatic origin, and no doubt they frequently originate in mental conditions such as worry, or overwork, and also in defective vision. Still, we are but very imperfectly acquainted with the links which connect excessive worry with pain in the head and vomiting: and it is I think probable that here, as in many other cases, popular opinion is based to a certain extent upon truth. Lately during the epidemic of cholera in Spain we have heard the same cry raised as in the Middle Ages, that the wells were poisoned, and the popular belief of the Middle Ages coincides with the results of modern scientific research in pointing to contaminated water as the source of disease,

1 Salkowski und Leube, *Lehre vom Harn*, p. 143.

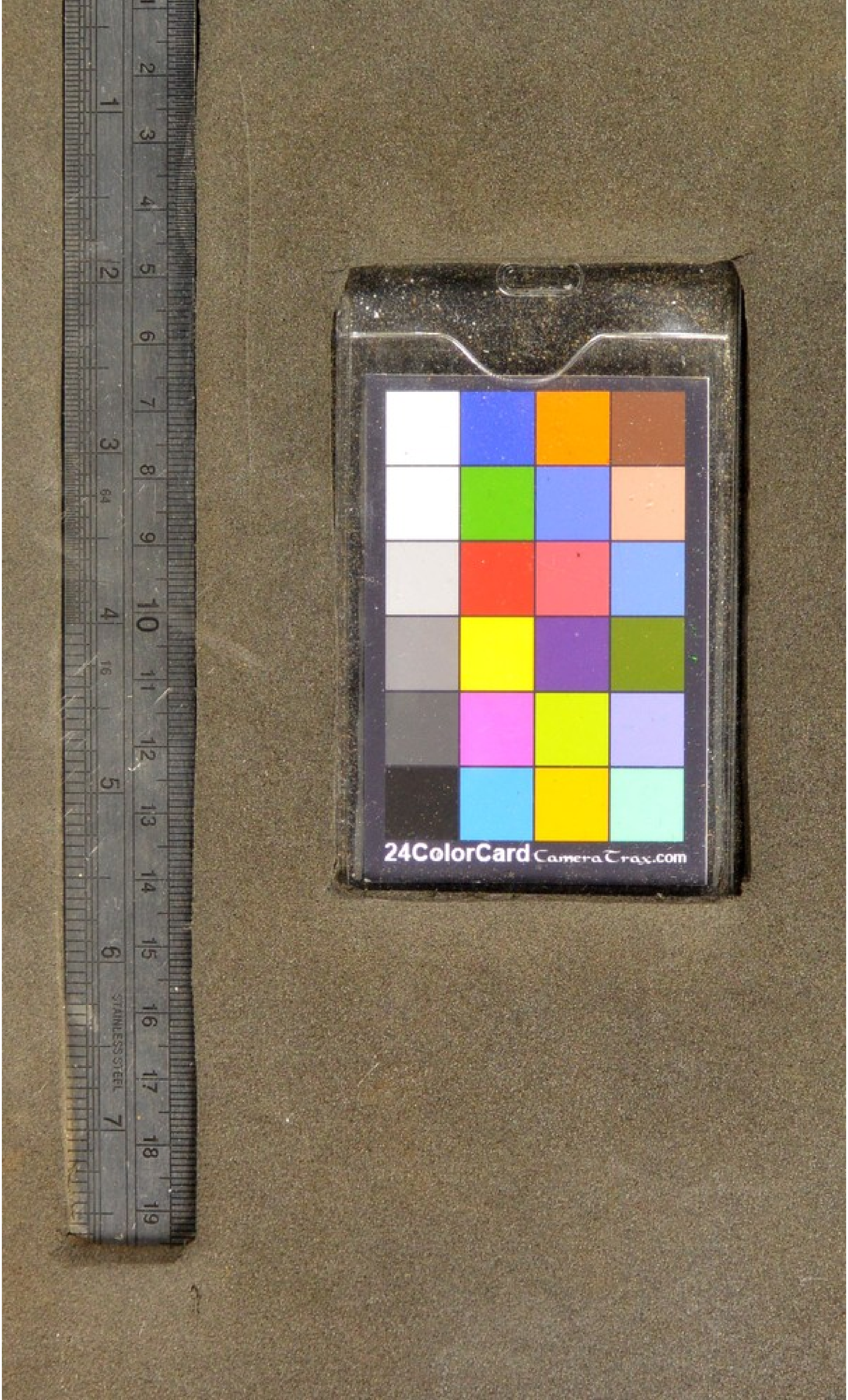
2 Brieger, *Weitere Untersuchungen über Ptomaine*, p. 70.

3 Quoted by Kobert, *Schmidt's Jahrb.* 1884, cciv. p. 13.

although the poisoning is due to the ignorance or carelessness which allows sewage to enter the wells, and not to the direct introduction of poison by design. Similarly popular belief in regard to headaches is, I think, not entirely mistaken in giving to them the term "bilious," for while they may originate in the central nervous system, the liver may play a not unimportant part in their actual production. In the case of a lady who consulted me a short time ago, I was a good deal struck by her observation, that she was always better after the vomiting although she brought up no bile whatever, and she was puzzled to know how the mere action of vomiting could do good. Her observation to a certain extent corresponds with my own experience, and I am inclined to believe that the relief experienced after the vomiting may be due, in part at least, to the emptying of the gall-ducts by the compression which the liver undergoes between the diaphragm and the abdominal walls in the act of emesis. The pressure under which bile is secreted is normally very low, and it is easy to see that if the bile should from any reason be more viscid than usual, mechanical pressure would be exceedingly useful, by tending to press the viscid bile, along with any alkaloid it may contain, out of the liver into the duodenum, and thus to prevent its re-absorption.

I do not mean to accuse the bile of being the primary factor in the production of biliary headache. I should be inclined to look upon it more as an accessory, and to attribute the symptoms rather to the presence in the bile of some alkaloidal substance which, on passing into the general circulation, gives rise to vascular disturbance and headache.

We must look to further observations upon the nature of the alkaloids formed by putrefaction; upon the effect of typhoid and other bacilli, on milk, eggs, beef-tea, and other foods used in typhoid fever, to a more exact investigation of the alkaloids formed in the intestine and found in the fæces and urine, and to experiment upon the action of aromatic substances formed in the intestine upon the liver, for further knowledge which may aid us in treating disease; but enough has been already done to show what important effects on the animal body are in all probability produced by the alkaloidal products of albuminous decomposition.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