THE USE OF ANTISEPTICS IN THE TREATMENT OF INFANTILE DIARRHŒA.¹

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DURING the last few years a considerable amount of attention has been directed to the various chemical changes which occur in the digestive tract as the result of bacterial activity, and certain facts have come to light which prove beyond doubt that many clinical phenomena, which formerly were either ignored altogether or regarded as symptoms of a fortuitous nature, must now be attributed to the direct absorption of organic poisons from the stomach or intestine. The various researches which have so materially contributed towards this discovery have also indicated that certain morbid conditions of the digestive organs which are usually assigned a simple etiology owe their origin in reality to diverse and often complex causes which are themselves intimately connected with abnormal fermentations of the food. In view of these facts it is not surprising to find that the principles which were formerly laid down for the treatment of disordered digestion have undergone a corresponding change, and that instead of employing sedatives or astringents for the relief of gastric or intestinal irritation, our principal efforts are now directed to control the immediate cause of the disorder by the exhibition of drugs which possess the power of inhibiting the processes of fermentation.

The question of gastro-intestinal antiseptics extends over such a wide field, and embraces so many subjects, that any attempt to deal with it in an adequate manner is beyond the scope of a single paper. I will therefore confine the few remarks I have to make to the antiseptic treatment of the intestinal dyspepsia of infants, the chief symptom of which is diarrhœa.

ETIOLOGICAL CONSIDERATIONS.

The researches of Escherich, van Puteren, and others have shown that, although at birth the contents of the digestive tract are sterile, bacterial infection is brought about within the first twelve hours of life through the medium of the atmospheric air which the infant swallows in large quantities. The various micro-organisms thus introduced into the system thrive and multiply in the mucus and undigested food which soon fills the intestine, and are constantly reinforced in numbers and diversified in species by the ingestion of contaminated milk or the swallowed secretions of the mouth. The danger which arises from these natural sources of infection is greatly increased by the fact that during infant life the gastric juice is incapable of exerting any decided control over microbial growth, owing to its comparative deficiency in free hydrochloric acid. Milk fermentation ensues from the presence of *B. lactis aerogenes* and the *B. butyricus*, which along with several other varieties of lesser importance are constantly found in the stomach of infants suffering from indigestion. The first-named converts the milk sugar into lactic acid with the precipitation of casein, while the latter changes a portion of the lactic into butyric acid, and in so doing liberates free hydrogen gas. The presence of these abnormal products in the contents of the stomach give rise to abdominal pain, distension, and vomiting, a series of symptoms which characterise the disorder known as acute dyspepsia.

The entrance of undigested and fermenting material into the intestine induces violent peristalsis, with the result that the infant suffers from colic and diarrhœa until the bowel has succeeded in ridding itself of its irritating contents. If proper means be taken to assist this effort of Nature and to prevent a recurrence of the disorder, the stools soon resume their normal appearance, and perfect recovery ensues. But if these evidences of digestive derangement are overlooked or neglected, and the child is constantly plied with food, each fresh supply of milk undergoes the same process of fermentation in the stomach, and hastens the advent of the second stage of the disorder—namely, gastro-intestinal catarrh. This inflammatory condition probably arises from direct irri-

tation of the mucous membrane of the digestive tract by the acid products of fermentation, and since it is always accompanied by a diminution in the secretion of hydrochloric acid, gastric digestion becomes greatly enfeebled, and the various bacteria are afforded an unlimited scope of action. Within a short period of time the intestine becomes affected in a similar manner, and the child begins to lose flesh and strength and to present all the symptoms characteristic of chronic intestinal catarrh. The third and last stage of the disease is marked by a more or less extensive cirrhosis of the mucous membrane of the digestive tract, often associated with the follicular ulceration of the colon. The diarrhœa continues and the stools are largely mixed with mucus or streaked with blood; the marasmus increases, and death finally ensues either from exhaustion or from some nervous phenomena due to the absorption of toxins from the alimentary tract. This sketch of the etiology of the infantile diarrhœa serves to emphasise three important facts. In the first place the disorder is a direct result of the activity of certain bacteria which produce abnormal fermentations of the food with subsequent inflammation of the stomach and intestines. Secondly, the intestinal derangement is primarily dependent upon gastric indigestion, and hence the symptomatic diarrhœa will not be overcome until the gastric disorder has subsided. Lastly, the prognosis in chronic cases depends upon the extent of the organic changes which have taken place in the digestive organs, and the influence they exert upon the assimilation of the food.

MEDICINAL ANTISEPTICS: THEIR ADMINISTRATION AND MODE OF ACTION.

Although the theory of intestinal antiseptics is comparatively modern, its practice dates from the earliest times. Thus the empirical value of emetics and purgatives in cases of dyspepsia obviously depends upon the fact that these measures serve to rid the system at once of the agents of putrefaction and their products; while in the routine treatment of diarrhœa by such drugs as calomel and subnitrate of bismuth, the same unconscious adoption of antiseptic principles may be discerned.

The various antiseptic drugs which are specially adapted for medicinal use can be roughly divided into two classes according as they are soluble or insoluble in water. The first group comprises such substances as carbolic acid, perchloride of mercury, lactic acid, hydrochloric acid, salicylate of sodium, and resorcine. The chief members of the insoluble class are naphthalin, β -naphthol, betol, benzol-naphthol, salol, the salicylates of bismuth and strontium, and calomel. In addition to the question of solubility there exists another and more important distinction between the members of the two classes. The soluble varieties possess germicidal and toxic properties in direct proportion to the dose in which they are administered, and since they are absorbed rapidly from the alimentary tract it is obvious that they can only exert their specific action in the stomach and upper part of the small intestine. The insoluble drugs, on the other hand, remain for the most part unaltered in the stomach, and therefore exert but little influence upon the fermentative processes which occur in that organ. In the intestine, however, the majority of them are subjected to chemical influences by which they are decomposed, with the ultimate production of secondary substances that exhibit both antiseptic and poisonous properties far in excess of the original drug. These latter remedies are accordingly reserved for cases where it is necessary to control bacterial activity in the intestine, and for this purpose they are administered in full doses at short intervals of time.

Hydrochloric acid inhibits the growth of most species of bacteria when it exists in the proportion of more than 0.17 per cent. (Miller). It is probable that in its natural combination with pepsin the acid not only kills but actually digests many bacteria, and in this manner serves to protect the intestine from the action of pathogenic organisms introduced with the food. The acid has been much extolled as an efficient antiseptic in cases of infantile dyspepsia, and is usually administered either in the form of 0.4 per cent. solution or as the *Pharmacopœia* preparation of the dilute acid. Its use is contra-indicated by the presence of gastric catarrh.

Lactic acid possesses less than one-fifth of the antiseptic

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power of the mineral acid aforementioned. It has been chiefly recommended by certain French physicians as a remedy for the green diarrhœa of infants, attributed by them to the presence of a chromogenic bacillus. It is most advantageously employed as a 2 per cent. solution, of which a teaspoonful may be given every two or three hours. This acid occasionally gives rise to gastric pain and vomiting, especially if the mucous membrane of the stomach be inflamed. It is excreted by the kidney in the form of lactate of sodium.

Carbolic acid is undoubtedly one of the most powerful germicides we possess, but unfortunately its medicinal value is considerably impaired by its unpleasant taste and poisonous character.

Although the presence of pyrocatechin in the urine does not necessarily indicate danger to life, it should always be regarded in the light of a warning, and the dose either decreased or the drug discontinued altogether. Carbolic acid can be administered to children either in the form of the pure acid (1 minim well diluted), or as the glycerine preparation (2 to 4 minims).

The use of perchloride of mercury is also somewhat limited on account of its toxic properties. In severe cases of diarrhœa it has been used with success when given in doses of $\frac{1}{8}$ to $\frac{1}{4}$ of a grain every two hours. It is rapidly eliminated by most of the excretory organs of the body.

Resorcin (metadihydroxybenzolum) is a crystalline powder, freely soluble in water, and possessed of a harsh sweet taste. Its solution is powerfully antiseptic, 0.4 of the substance inhibiting the growth of all the micro-organisms which are found in the stomach and intestine. It is rapidly absorbed by the mucous membrane of the alimentary tract, and can be detected in the urine by means of perchloride of iron (violet colour) within a short time of its ingestion. In moderate doses resorcin is devoid of toxic properties, but when a drachm or more is given at a time giddiness, headache and sweating are apt to supervene. For these and other reasons, which will be mentioned immediately, I consider it one of the most useful remedial agents we possess for the treatment of infantile diarrhœa.

Among the insoluble aromatic compounds of the carbon series naphthalin has, perhaps, enjoyed the greatest amount of reputation. Although insoluble in water, a certain amount is absorbed by the intestine, and is excreted by the kidney in the form of naphtho-sulphite of sodium, thereby producing a brownish-black coloration of the urine. When mixed with nutritive media this substance exhibits comparatively feeble antiseptic properties, as much as 1.5 per cent. being usually required to inhibit the growth of the intestinal bacteria. Naphthalin possesses a powerful and disagreeable smell, and in certain cases its administration is followed by renal and vesical irritation. The dose for a child is from 2 to 5 gr., either mixed with sugar or suspended in some sweet emulsion.

Naphthol is a powerful germicide when it exists in a proportion greater than 0.03 per cent. It is only slightly poisonous, but its taste and smell are unpleasant. It has been used with success in cases of infantile diarrhœa, about 2 gr. being given every four hours either mixed with white sugar or dissolved in olive oil and emulsified.

Salol (salicylate of phenol) is a white, tasteless powder which remains unchanged in the stomach, but in the duodenum is rapidly split up into phenol and salicylic acid, the latter of which can be detected in the urine within seventy minutes of its administration. In test-tube experiments this substance only retards the growth of bacteria when it exceeds 0.6 per cent. of the medium. To infants 10 gr. may be administered in divided doses during the course of the twenty-four hours.

Benzol naphthol is a tasteless powder, which in the intestinal canal becomes decomposed with the liberation of naphthol and benzoic acid. The latter is excreted in the urine, partly in combination with alkaline bases, and partly in the form of alkaline hippurates. This substance is not poison when given in moderate doses, and it is therefore of considerable value in case of infants and young children, to whom it may be administered in doses of 30 grains per diem.

Iodoform was formerly advocated as a medicinal remedy, but it has now been to a great extent replaced by the before-

mentioned preparations. Its antiseptic properties are probably greater in the intestine than laboratory experiments would indicate (0.3 per cent.), since it undergoes partial decomposition in the bowel with the liberation of free iodine. In combination with charcoal, it has been strongly recommended by Bouchard as a means of diminishing the toxicity of the urine and fæces.

The salicylates of bismuth and strontium both undergo chemical changes in the intestine with the formation of salicylic acid and the corresponding metallic sulphides. The acid exerts a powerful antiseptic influence upon the contents of the bowel, and is slowly eliminated by the kidney. The sulphide of bismuth betrays its presence by the characteristic blackening of the motions. Both preparations are tasteless and insoluble, and may be given to infants in doses of 1 to 3 gr. every four hours. It is usually stated that the salicylic acid exerts an irritant action upon the kidney, and that the drugs which cause its elimination in the urine are contraindicated in cases of albuminuria. This objection is, I believe, more theoretical than real.

Calomel is an excellent example of that class of remedies which owe their antiseptic properties to a change in their chemical composition occurring after ingestion. It is probable that the subchloride of mercury when given in minute doses is partially converted in the stomach into the perchloride, and in the intestine into the sulphide. It is by far the most reliable remedy we possess for acute cases of diarrhœa in infants when administered in fractions of a grain at frequent intervals.

RESULTS

In the selection of an appropriate drug for a child several factors have to be taken into consideration which in the case of an adult can safely be neglected. Substances which possess a nauseous taste or offensive smell are hardly tolerated by a child even when mixed with an excess of sugar; and hence naphthol, β -naphthol, and iodoform can seldom be prescribed with success. Again, absorption takes place so readily from the alimentary tract of an infant that it is often impossible to obtain any degree of intestinal antiseptics from the use of perchloride of mercury and the phenol compounds without running great risk of poisoning the patient in the process. Lastly, powders like charcoal, which have to be administered in large bulk in order to produce any effect at all, are obviously inapplicable to the treatment of disease in infants. In the majority of cases, therefore, our choice is limited to the tasteless and comparatively non-toxic powders, such as calomel, benzol-naphthol, and the salicylates of bismuth and strontium, or to the soluble antiseptics like resorcin and the acids. During the last three years I have used the various medicinal antiseptics in more than 500 cases of digestive disorders in children which have come under my notice at the Evelina Hospital and elsewhere. The results which have accrued from their use in cases of infantile diarrhœa have been so satisfactory that for more than twelve months I have never once had occasion to resort either to astringent drugs or to opium, whilst in almost every instance where these latter remedies had been previously tried without effect the substitution of an antiseptic was at once followed by complete success. Acute dyspepsia is readily cured by dietetic treatment combined with the use of castor oil or an emetic. Antiseptics are only necessary when the disorder has already continued for several days, and has resisted the simpler methods. Under these conditions calomel is of the utmost value when administered in doses of one-sixth to one-third of a grain every three or four hours. Hydrochloric acid has been extolled by many authorities, but, according to my experience, the mineral acid more often does harm than good. It is most serviceable when all acute symptoms have subsided, and the child is suffering from weak digestion as the result of catarrhal process. It may then be combined with pepsin with great advantage.

It is in cases of chronic diarrhœa due to fermentation that the systematic employment of antiseptic drugs proves of the greatest value; and for this purpose the insoluble substances which act exclusively upon the intestine are usually recommended. This, however, is a mistake. The disorder always commences in the stomach, and is most easily controlled by the administration of remedies which exert their specific action within that organ. Formerly I was wont to employ

carbolic acid for this purpose in all cases of infantile diarrhoea, but its hot taste and unpleasant smell, as well as the occasional occurrence of carboloria, has made me transfer my allegiance to resorcin. This drug has the advantage of being extremely palatable to children, devoid of toxic properties when given in ordinary doses, and very inexpensive. According to the *Pharmacopœia*, the dose of resorcin is 1 to 5 gr., and it is probably on account of this insufficient dosage that the value of the remedy has been so much overlooked. As a matter of fact, the drug produces no ill effects in an adult unless the dose exceeds a drachm, and I have long been accustomed to prescribe 3 gr. every four hours to infants only a few weeks old without the least ill effect.

In cases of diarrhoea the first effect of the drug is usually noticeable after the third or fourth dose, when the motions decrease in frequency and in amount, the dejecta at the same time acquiring a more natural appearance and losing their excessive fetor. At the end of the second day the diarrhoea has generally ceased, and is not infrequently replaced by obstinate constipation. I have before me the notes of 120 cases of intestinal dyspepsia in infants and young children which have been treated in the manner described. Of these, in 53 per cent. the disorder had lasted from one to two weeks, in 34 per cent. from two to four weeks, in 10 per cent. from four to eight weeks, and in the remaining 3 per cent. for a period of more than two months. Out of the entire number in only nine instances did the diarrhoea continue after the treatment had been pursued for a week, the majority ceasing within three days. Of these nine refractory cases two were instances of cholera infantum, both of which succumbed within a short time of being brought to the hospital; in one case tuberculous ulceration of the intestine was found to exist after death, while the remaining six, most of which were very chronic in their nature, were rapidly cured as soon as benzonaphthol or salicylate of bismuth were added to the original mixture. These results go to prove that when given in sufficient quantity resorcin constitutes a reliable remedy in cases of infantile diarrhoea arising from fermentative processes in the stomach and intestine. When, however, the disorder has lasted for a long time and follicular ulceration of the large intestine exists, the drug may be advantageously supplemented by those remedies which exert their antiseptic properties in the intestine. Benzol naphthol is particularly valuable in this connection since it is but slightly toxic, but in order to prove effective it must be given in full doses at short intervals. Thus in some cases where the symptoms were obstinate I have prescribed as much as 40 gr. to a child during the course of twenty-four hours with only the most excellent results. My experience with the most recent antiseptic, the salicylate of strontium, has not been altogether satisfactory, and I have been unable to convince myself that it possesses any superior advantages over the corresponding salt of bismuth.

THE ATROPINE GROUP:

AN EXPERIMENTAL AND CRITICAL NOTE.¹

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SOME twelve months ago, I had under my care for a considerable period, a lady of 25, who suffered from repeated attacks of renal colic in whom a $\frac{1}{2}$ gr. of atropine sulphate (along with $\frac{1}{2}$ gr. morphine hydrochlorate) although always relieving the distressing conditions, produced unpleasant flushing of the face, dryness of the throat, and confusion of the senses. Having read of scopolamine being free from the disagreeable properties of atropine just named, I thought I might be able to get all the advantages of atropine with none of its disadvantages. I resolved to try the drug for myself, but after trial I found it differed little or not at all from atropine. Previous acquaintance with hyoscine taught me that it was little different from atropine, and after some experiments with daturine and duboisine I was led to extend my studies of the whole atropine group, and to read up the literature for the past twenty years, hence this paper.

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To the student of pharmacology no group of bodies is more confusing than the so-called mydriatic alkaloids known by the names of hyoscyamine, hyoscine, daturine, duboisine, scopolamine, and atropine, etc., all of which possess the property of dilating the pupil. A vague examination of them might lead one to the belief that each had some peculiar action of its own, but closer examination and increased knowledge show them to be very closely related if not identical one with another. True their sources are varied, but reasoning by analogy we know that tea, coffee, guarana, Paraguay tea and kola-nut are all very widely different plants, and yet they all contain one common alkaloid, theine, and not each a different base as at one time supposed.

The literature of the group of the atropine bodies is most interesting, because it shows the conflicting views of authorities; but as one comes to the present period it further shows a tendency to the view that we have only one or two bases to deal with. One other point it teaches us is that we cannot clear up the difficulty from the chemical side alone, but must call in the aid of pharmacology and therapeutics. With regard to Gerrard's test for the mydriatic group, I find after repeated trials that we do not, as is often supposed, get a yellow colour with one and a red colour with another member of the group, but with a trace of any one of them an alcoholic solution of mercuric chloride heated gives a yellow, while an appreciable quantity of any one of them gives a bright red colour of red oxide of mercury. The test is difficult to apply, and failures to obtain colour reactions with certain members may be accounted for in this way.

HYOSCYAMINE.

Whether hyoscyamine be identical with atropine or no one thing is certain—that they are very closely related; for in 1880 A. Ladenburg converted hyoscyamine into atropine, and in the following year the same authority found that both bases split up into tropic acid and tropine. Further comparisons show both to give a bitter almond odour with potassium bichromate and monohydrated sulphuric acid, and both, when heated with nitric acid and afterwards treated with alcoholic solution of caustic potash, become of a violet colour. Chemically so far, then, they would appear to be identical, and pharmacologically I do not know if we can distinguish between them.

DUBOISINE.

The introduction of duboisine about the year 1878 by Bancroft, Holmes, Gerrard, Ringer, and Tweedy stimulated research, and soon it was found that it was not a new base, but only an impure atropine. At this time A. Ladenburg gave it as his opinion that we had only three mydriatic alkaloids—namely, atropine, hyoscyamine, and hyoscine agreeing in formula and in decomposition products. Later Ladenburg so far modified his views as to believe only two bases exist—namely, atropine and hyoscyamine, and these are isomeric and very closely related.

DATURINE.

The introduction of daturine led to disputes amongst authorities. Some believed it to be identical with hyoscyamine, while A. Ladenburg considered daturine, duboisine, and hyoscyamine as identical. In the same year (1880) E. Schmidt said he failed to detect the difference between daturine and atropine. Deduction from this makes atropine and hyoscyamine identical. Passing to the year 1885 we find E. Schmidt saying atropine and daturine are identical, and in this view he is joined by Ladenburg.

HYOSCINE.

Coming to hyoscine we have seen that A. Ladenburg had so modified his views as to regard this body as not a different base from atropine or hyoscyamine. Pavloff in 1889, in summing up the pharmacology of hyoscine, regarded it as differing from atropine only in that it (hyoscine) diminished the irritability of the brain. Bender in 1892 looked upon hyoscine and scopolamine as identical, while in 1893 A. Ladenburg disputed the identity of the two. In the same year E. Schmidt said the so-called Ladenburg's hyoscine was really scopolamine, and in this view he was supported by O. Hesse.

SCOPOLAMINE.

In 1889 the alkaloids from both the Austrian plant and from