struction of the formulæ of compounds, and in the arrangement of their strengths. Considerable advantage would ensue if the idea could be carried out. Much interest had been shown in the question of dosage, and two opposite suggestions had been made. Dr. Mahomed would like to see an approach to symmetry in the strength of the preparations, that is, in the amount of the drug contained in them; this would, of course, mean that the doses would vary more than they now do. Other speakers had suggested that doses of similar kinds of preparations should be rendered more nearly alike than they now are; this would mean that the amount of drugs contained in such preparations would vary more than they now do. Dr. Leech preferred the latter plan, because if, as seems now possible, the most important preparations can be standardised, it will be easy to determine the exact amount of the active principles of a drug in each dose administered, and this, for the purpose of exact comparison of effects, would be more useful than knowing how much of the crude drug was contained in the preparation. He did not think Dr. Neville Wood's plan would be satisfactory, because the dose of any drug must be graduated to the patient and the ailment. It was not sufficient to say the maximum or minimum dose should be given, or an intermediate one. The dose had to be in many cases increased or decreased by degrees to suit the conditions of the case, and such additions and subtractions could not be made without a knowledge of the real amount given. As Dr. Bradbury had remarked, the dosage in the present *Pharmacopœia* would have to be revised, but it was manifest, considering the variation in views which had been expressed both here and elsewhere, that this revision would prove no easy task. The suggestion that the strength of hydrocyanic acid should be 1 per cent. instead of as at present seemed feasible. Dr. Talfourd Jones's views regarding morphine suppositories also called for serious consideration, and so did his suggestions for new suppositories. The defects to which Dr. Charteris had called attention, so far as regards tests, were deserving of consideration. The question of the value of introducing active principles, to which Dr. Carter and Dr. Stockman had alluded, was, as Dr. Stockman had pointed out, one which would probably receive different replies as time advanced. Doubtless the most exact method of giving drugs would be to determine accurately the amount of each active ingredient in the best specimens of a drug, and then give the active ingredients mixed in their exact proportion, for it seemed very probable that in some specimens of a drug the active principle might at times vary in relative amounts, and the same results, therefore, would not always follow the administration of a drug. But in the present state of chemistry and pharmacology this could not be done. It did not, however, appear impossible that at some future time active principles might be alone used.

THE ACTION OF BETA-NAPHTHOL AND BISMUTH SUBNITRATE AS INTESTINAL ANTISEPTICS.¹

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THE investigation to determine the antiseptic value of β -naphthol and bismuth subnitrate was undertaken because, like most other intestinal antiseptics, they are largely used in intestinal troubles supposed to be of bacterial origin by one class of practitioners, while there is a very important class that considers any such attempt as simply futile, if not dangerous, to the patient.

Diseases of the type of cholera, dysentery, typhoid, summer diarrhoea of children, which are most probably due to bacterial infection, or are at least invariably associated with an enormous increase of one or several types of micro-organisms, are daily being treated with one or another kind of antiseptic that happens to be the latest favourite.

¹ Read in the Section of Pharmacology and Therapeutics at the Annual Meeting of the British Medical Association, held in London, July-August, 1895.

Creasote, carbolic acid, perchloride of mercury have been at one time or another used extensively and dropped either on account of their extreme toxicity, or because the clinical results have proved to be unsatisfactory in some hands.

One of the recent additions to this class of drugs is β -naphthol, a coal-tar product which M. Bouchard introduced to the medical profession in 1887 as a valuable intestinal antiseptic for typhoid fever and summer diarrhoea of children. Since that time, this drug has been used extensively with varying results.

The following experiments were consequently undertaken to determine definitely the real value of β -naphthol as an intestinal antiseptic. In the course of the experiments bismuth subnitrate was used at first as an indicator to determine the completion of antiseptics as is suggested by M. Bouchard. However, some observations made with bismuth subnitrate alone in the presence of putrefactive bacteria showed that this drug is not quite inert, but that it is capable of modifying, hindering, or destroying them.

Thus the paper treats of β -naphthol primarily and bismuth subnitrate secondarily. The observations were both chemical and bacteriological. Chemical experiments consisted in estimating the amount and ratio of alkaline and aromatic sulphates present in urine of man before, during, and after taking either of the drugs separately or together. The amount of urea was also estimated at the same time to see how far the body was kept on nitrogen equilibrium. The method of administration was always *per os* in the form of powders.

In the first series of experiments with β -naphthol, which lasted for nineteen days 1 g. was taken twice daily during twenty-four hours. The first dose was taken at breakfast, and the second at dinner time. The drug was taken during the last twelve days of the experiment, while during the first week the normal ratio of the sulphates was determined. The day and night urine was analysed separately. The day urine was collected from 9 A.M. till 7 P.M., and the night urine from 7 P.M. till 9 A.M.

The second series of experiments lasted for thirty-seven days. The first day's urine was tested for the normal ratio. On the succeeding seven days 0.5 g. of bismuth subnitrate was taken twice daily. The first dose was taken at breakfast and the second at dinner time. During the next week 1 g. of bismuth subnitrate was taken thrice daily. The third dose was taken at lunch time.

During the next four days 1 g. β -naphthol in the morning and evening, with bismuth subnitrate, which was continued in 1 g. doses thrice daily. During these days the urine was analysed daily except on Saturdays and Sundays. The urine was again analysed on the sixth day after the last day of β -naphthol and bismuth subnitrate, and again for three days at the end of another week.

The general result of these experiments was to show an increase of aromatic sulphates during the time when β -naphthol was taken either alone or with bismuth subnitrate. The total sulphates did not vary much during the same period as compared with normal periods. On the other hand, the alkaline sulphates were always diminished under the influence of β -naphthol. Consequently, the ratio between alkaline and aromatic sulphates, which was 10:1 during the normal periods, increased to 10:2 on an average, and on one occasion even went up as high as 10:4.

The general health remained the same during these periods, except that on the last day of bismuth subnitrate and β -naphthol, griping and slight looseness of bowels occurred. The urine did not show any other alteration except that it had a greenish violet fluorescence during the time β -naphthol was taken, and on addition of a few drops of it to 10 c.cm. of pure sulphuric acid it acquired a dirty green colour, as is stated by Hoppe-Seyler, thus proving the presence of β -naphthol in the urine.

From these experiments it is not possible to say how far β -naphthol serves to diminish the aromatic sulphates, because that is most probably masked by the drug itself, which is excreted as an aromatic sulphate at expense of the alkaline sulphates. The aromatic sulphates, however, diminished considerably on stopping β -naphthol, and the ratio fell as low as 10:0.83. During the time when 1 g. bismuth subnitrate was taken daily the alkaline sulphates increased at the

expense of the aromatic while the total sulphates remained the same. The ratio of alkaline to aromatics fell from 10:1.2 to 10:0.8. However, the reverse happened when the dose was increased to 3 g. per diem; on one occasion the ratio increased to 10:1.58. During the time when the larger dose was taken there was slight constipation.

The bacteriological observations consisted of the ordinary test tube experiments with bismuth subnitrate and β -naphthol: 1 mg. to 1 cg. of β -naphthol was added to 10 c.cm. of sterilised glucose gelatine, and set in the indicator for a week before using them for inoculation. Most of the tubes that had less than 6 mg. of β -naphthol developed a growth, that is, 0.06 per cent.; β -naphthol tubes remained sterile. Similar bismuth subnitrate tubes were also prepared and treated in the same manner. None of them were found to be contaminated. Those tubes that remained sterile were used for subsequent inoculations from either pure cultures of cholera bacillus, the vibrio Metchnikovii, bacillus coli communis, and the typhoid bacillus, or from mixed growths of putrefactive bacteria from infusion of meat.

These mixed cultures consisted of different forms of micro-organisms, and one of the most evident results of their growth was the evolution of sulphuretted hydrogen, which could be easily detected by the reduction of bismuth subnitrate.

Thus the addition of bismuth subnitrate to a culture of these produced two effects. First, it was converted into a sulphide; and, secondly, the reaction of the culture medium, which was strongly alkaline before the addition of bismuth subnitrate, became strongly acid in a short time. Returning to the tubes to which the antiseptics were added previous to inoculation, it was found that tubes to which 8 mg. to 1 cg. of β -naphthol was added, that is, those that had 0.08 per cent. to 0.1 per cent. β -naphthol, always remained sterile, while β -naphthol in smaller amount was not invariably able to prevent a growth. In small doses (1 mg. to 3 mg.) it was not able to prevent the evolution of sulphuretted hydrogen. The reaction of these tubes was strongly alkaline. The subcultures from these tubes always grew feebly. The bismuth tubes that had 1 cg. for 10 c.cm., that is, 0.1 per cent., remained sterile after inoculation, while scanty growth occurred in those that had even 8 mg. with reduction of the bismuth. The reaction in these cases was acid.

Subcultures from these tubes either could not be obtained or were very feeble. Tubes with still less bismuth subnitrate showed a copious growth and reduction of bismuth. Subcultures from these were easily obtained. The experiments with the specific micro-organisms mentioned above showed almost identical results. All of them are capable of reducing bismuth subnitrate.

Indol reaction in the case of bacillus cholerae, vibrio Metchnikovii, and bacillus coli communis, and also in the case of mixed cultures, could not be obtained with any of the tubes that had bismuth subnitrate, although subcultures from the weaker tubes could be obtained which were capable of giving the reaction.

These tests could not be applied in the case of β -naphthol tubes because β -naphthol alone gives almost an identical colour reaction. All these facts point to the conclusion that both β -naphthol and bismuth subnitrate have the power of preventing or hindering the growth of micro-organisms, and that β -naphthol is the stronger of the two in some cases. The safest dose for β -naphthol is about 8 in 10,000; while for bismuth subnitrate it is 10 in 10,000.

These experiments only show how far the growth of these microbes is prevented or delayed in test tubes, when the antiseptic is added previous to the germs. However, we must recognise the fact that in determining the value of an intestinal antiseptic the microbes are already there in enormous numbers before the antiseptic could be added, and that every meal adds to that number.

Two sets of experiments were therefore undertaken to see how far these drugs could act as intestinal antiseptics. The first series consisted of determination of the approximate number of colonies present in the contents of the different parts of the alimentary canal of dogs, after feeding them for several days on the same kind of food. These numbers were compared with those obtained from dogs treated with bismuth subnitrate, β -naphthol, or both of them combined.

The total contents of each part were diluted with about half a litre of sterilised water. The weight of the flasks and the weight of the water being previously determined, the weight of the intestinal contents was easily ascertained. This gave the ratio of dilution. The contents of the whole canal were divided into five parts, namely, those of the stomach, the duodenum, the upper half of the small intestine, the lower half of the small intestine, and the large intestine; 0.1 c.cm. from these flasks was added to 20 c.cm. of nutrient gelatine for plate cultures. However, it was soon found that the contents of the lower part of the small intestine and of the large intestine contained an enormous number of liquefying micro-organisms. Consequently, for the later experiments agar was substituted, and the contents of the last two parts were further diluted. The faeces of the dogs which were treated with β -naphthol and bismuth subnitrate or with the latter alone were daily observed to see whether the blackening due to the reduction of bismuth subnitrate could be used as a reliable indicator for completion of intestinal antiseptics, as is suggested by M. Bouchard.

The results were unfortunately varying. The bismuth dogs as a rule passed black faeces for some days, then there would be no blackening for a day or two; nevertheless, the colour reappeared although bismuth was continued throughout the period. The faeces of the β -naphthol and bismuth subnitrate dogs showed the same variations.

Again, it was found that the plate cultures of two normal dogs were not able to reduce the bismuth subnitrate. On the other hand, plate cultures from some of the β -naphthol dogs reduced the bismuth at once. However, the number of colonies gave more satisfactory results. Dogs that were treated with β -naphthol and bismuth subnitrate showed considerable reduction of the colonies whole throughout the tract. Simple β -naphthol showed a similar reduction. The bismuth subnitrate produced a reduction in the number in the upper parts of the tract, while the colonies in the lower parts were hardly reduced.

The great disturbing factor for making a satisfactory comparison between different animals was the nature of food and the amount of contents found, as the number of colonies always varies with the food and the quantity of the contents. Dogs fed on biscuit showed an excessively large number as compared with those fed on meat alone. Again, the colonies from very scanty contents were very few even relatively to those from a tolerably fair amount of contents. Thus, for making any satisfactory comparison between the colonies from different animals these two disturbing factors have always to be taken into consideration.

The second set of experiments consisted in taking 50 c.cm. of the diluted contents of the large intestine of five dogs, and adding 0.5 g. of the antiseptics either singly or together, and these were left in the incubator at 37° C. for several days. Both the antiseptics being scarcely soluble in water, the flasks were shaken frequently. Subcultures from these were made daily to see whether the contents were sterilised or not. None of the β -naphthol flasks were sterilised even after thirty-five days.

After the sixteenth day all the bismuth subnitrate flasks were sterilised, while flasks having both the antiseptics showed very feeble growth at the same period. Subcultures were made in glucose-gelatine tubes and put in the incubator. Control flasks having none of the antiseptic showed a growth during the whole period. One of these five dogs was a normal one; one had bismuth subnitrate for twelve days; two dogs had β -naphthol for sixteen days; while one had bismuth subnitrate and β -naphthol for twelve days.

These experiments show that bismuth subnitrate is more powerful as a germicide than β -naphthol when large doses are used. However, internally β -naphthol appears to act better than bismuth subnitrate. The reason for this discrepancy is probably to be found in the fact that although bismuth subnitrate is the stronger antiseptic, its value is lowered on account of its constipating property. The explanation of the fact that in the test-tube experiments β -naphthol was found to be somewhat stronger than bismuth subnitrate is to be sought probably in the mode of action of bismuth subnitrate.

From the fact that this salt is easily converted into a sulphide in the presence of organisms that produce sulphuretted

hydrogen or some other sulphide, we might assume that nitric acid must be liberated at the same time. This is rendered highly probable by the fact that cultures that are alkaline before addition of bismuth subnitrate become acid after some time. However this acidity is not due to free nitric acid, but to some organic acid which the liberated nitric acid sets free from the culture medium.

However, to obtain some positive proof for the assumption the following experiment was performed. Bismuth subnitrate, when shaken up with boiled distilled water, gives a neutral reaction for about five minutes, after that it changes to acid. Ultimately it becomes so markedly acid that Congo red paper shows the presence of free nitric acid. Heat favours the reaction. This reaction gives a satisfactory explanation of the phenomena described above.

Why those flasks to which both drugs were added should not be sterilised earlier than those to which bismuth subnitrate was added alone is rather difficult to account for. A possible explanation is that the liberation of nitric acid is either delayed or retarded in the presence of β naphthol.

In the foregoing we have tried to state the facts as concisely as possible, and have avoided drawing any conclusions from them.

ON THE DIGITALIS GROUP AND THEIR USE IN THE TREATMENT OF DISEASE OF THE HEART.¹

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THE digitalis group comprises a considerable number of plants of different botanical families and of varying activities, ranging from the deadly upas to the comparatively innocuous convallaria and adonis, all of which have an action on the heart more or less resembling that of the plant which gives its name to the group.

The fundamental action of the members of this group is to increase the elasticity of muscular fibre so that it expands more slowly and contracts more perfectly. The effect of this upon a hollow muscle like the heart is that it dilates more slowly and empties itself more completely; residual accumulation is thus prevented and any dilating influences are counteracted. The heart is affected earlier and more powerfully than the other muscles because the blood passes so frequently through it that it receives a larger dose of the drug within the same space of time. For a similar reason the muscular coat of the arterioles also gets a disproportionate share of the drug and is early and strongly affected, though not nearly to the same extent as the heart, as the arterioles are only stimulated by the comparatively small quantity of blood passing to their own district. The more perfect contraction of the heart throws a larger blood wave into the arteries, and as the effect of the increased elasticity of the muscular coat of the arterioles is to keep their calibre contracted, the blood escapes more slowly into the veins, it accumulates within the arteries and the blood pressure within them is raised. The effect of this is that every muscle in the body, and amongst them the myocardium, is flushed with blood at an increased pressure and their nutrition and energy are improved and augmented by a more perfect metabolism.

The action just described is that of digitalis itself; it seems probable that, besides the general action on the muscles, each of the members of this group has a common action on the heart, coupled with specific differences of its own. We know, for example, that digitalis acts powerfully on the heart and arteries, and less so on the uterus and bladder; and that ergot acts energetically on the uterus and bladder, and less so on the heart and arteries; and Professor Fraser tells us that strophanthus acts powerfully on the heart, and but slightly on the muscular fibres of the arterioles. Fraser claims this as an advantage in favour of strophanthus; it seems to be a very doubtful advantage, and it distinctly shows that the action of strophanthus specifically differs from that of digitalis. From the absence of any marked constriction of the arterioles, any rise in the blood pressure follow-

ing the use of strophanthus must be due to ventricular action only; it is not, therefore, persistent, and can only feebly affect the muscular metabolism. We need not, therefore, wonder that when the action of the drug is withdrawn the heart is not found to have received permanent benefit, but remains pretty much as it was. Strophanthus forces on the ventricles an increase in the strength and duration of the systole, which ceases with the action of the drug. It acts as a cardiac poison and not as a cardiac tonic. In cases of valvular lesion with ruptured compensation and dropsy, strophanthus acts doubtless as a diuretic, but in this respect it is uncertain. Apart from the experience of myself and others, the very discrepancy in the dose prescribed indicates this, for while some find 5 minims of the tincture every four hours amply sufficient, others find as much as 10 or more minims every two hours to be required. Past history and present experience alike teach us that to restore a ruptured compensation in cases of valvular lesion drugs are not always required. If such a patient is put to bed, the recumbent posture at once reduces the work of the heart by ten or twelve beats per minute, and this, coupled with warmth and good food, is sufficient to rehabilitate the hearts of most hospital patients, to raise their blood pressure, increase the flow of urine, and drain their cavities. The addition of a few doses of strophanthus will not prevent this improvement, even if it does not materially assist it.

Strophanthin has, however, two advantages over digitalin; it is readily soluble in water, and it is rapidly absorbed; it is thus available for hypodermic injection, and, as it acts with great rapidity, it may be of service when administration of any drug by the mouth would be of little use. There may thus be circumstances in which strophanthin is to be preferred to digitalin, though it may be doubtful whether the hypodermic injection of ether is not more likely to be more useful than either, when the failing heart stands in need of an immediate fillip.

Strophanthus is the only member of this group which has any pretensions to rival digitalis, yet it is so much more uncertain in its action, and so devoid of tonic properties, that we are not tempted to displace in its favour our own indigenous drug.

Dotted all over our upland pastures there is no nobler plant in our indigenous flora than the digitalis purpurea, and there is no more potent benefactor to mankind among the many constituents of our materia medica. For more than a hundred years digitalis has been known as a sovereign remedy for dropsy, but it is only within the last twenty years that its true properties have begun to be recognised. And even yet the profession are hampered in its use by the continued prevalence of the idea that digitalis is a most powerful but dangerous sedative to the heart—an idea that dates from those not so far back days when digitalis was supposed to possess a number of distinct actions, all more or less antagonistic to one another. Now we know that digitalis is a tonic to the muscular fibre, and that it acts chiefly on the heart and on the muscular coat of the arterioles. From this action flow all the benefits we obtain from this drug, while any unpleasantness that may happen to follow its employment is due to the effects of an overdose, and for this the prescriber is to blame and not the drug.

Digitalis in every form is absorbed with difficulty and only slowly excreted, hence if the dose is repeated at too short an interval the drug accumulates within the system, and ere long symptoms of poisoning appear. This faculty of accumulation digitalis shares with many other drugs. Unfortunately for its own reputation its sphere of usefulness lies among a class of cases in which sudden death is no uncommon occurrence, and for many a day any sudden death in a patient taking digitalis was always ascribed to the cumulative action of the drug quite irrespective of the dose administered. Even yet there is an idea of danger connected with this drug which hinders the usefulness of this invaluable remedy. Deaths from digitalis poisoning in those otherwise healthy are amongst the rarest of occurrences; only a very few are on record. A full account of one has been published in which 211 grains of the powdered leaves were taken within five weeks before the fatal result.² Sickness, diarrhoea, faintness, and slow pulse had prevailed during fully four of these

¹ Read in the Section of Pharmacology and Therapeutics at the Annual Meeting of the British Medical Association, held in London, July-August, 1895.

² Köhnhorn, *Vierteljahrsschrift für gerichtliche Medizin*, 1876, S. 278.