THE ACTION OF URINARY ANTISEPTICS.

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THE treatment of infections of the genito-urinary tract by means of medicines administered by the mouth presents many inherent difficulties, and only very little help in overcoming these can be got from the kind of information yielded by experiments carried out with test-tubes and bacterial cultures. The conditions in the two cases are so widely different that the real value of any remedy can only be gauged from clinical experience of it. In the first place it is impracticable to administer to patients very powerful germicidal poisons to be excreted in the urine, and those which we can use are so chemically altered and detoxicated in the body that they reach the urine in a greatly weakened form. Further, fresh supplies of active living organisms are constantly contributed from the deeper tissues of the infected urinary passages, or from the prostate or seminal vesicles, or from other places to which the drugs may hardly penetrate, and thus the infection may be kept up and renewed indefinitely. Further, once the urine is infected it forms a favourable culture medium which is continually being reinforced by the blood, pus, and general organic debris usually present, and these elements may in addition adsorb and bind a considerable part of the remedy and thus further diminish its effective action on the bacteria. The formation of ammonia from urea in some cases and the obscure chemical interchanges always going on among the urinary salts must also constitute a disturbing factor, while frequent emptying of the bladder may leave from time to time a quite inadequate supply of the drug to cope successfully with the bacterial growth. Like many of our most trusted remedies, such as digitalis, potassium iodide, arsenic, and quinine, for example, urinary antiseptics show their desired effects only under conditions of disease, and these effects could not have been deduced from a study of their action on healthy men or animals. Most of these disturbing elements are absent in observations carried out with test-tubes, and hence the problems connected with the real practical value of urinary antiseptic drugs must depend on clinical rather than laboratory solution. There are other considerations which further accentuate the

differences. The kidney normally excretes from the blood-stream coliform and other organisms, and healthy urine and urinary passages seem to be very immune to infection from this source; but the presence of any local organic lesion at once weakens the immunity and at the same time renders treatment much less effective and more difficult to carry out. It is, therefore, an essential part of any drug treatment to deal as radically as possible with enlarged prostate, urethral stricture, stone, or any other lesion which may be present. Another great and important element of success is early treatment in order to prevent deep infection of the tissues, and equally important is prolonged treatment carried out until the infection is eradicated and not merely ameliorated. I have often noticed that when *B. coli* and staphylococcic infections of the bladder have become chronic there occurs almost complete local immunity, so that the patient experiences no discomfort although the urine may be swarming with organisms; and owing to there being no complaint and no symptoms these cases are frequently overlooked. It is often difficult to induce such patients to persevere with treatment, although it is very essential they should do so, as there is always present a greater or lesser amount of systemic poisoning besides the risk of exacerbations. Such individuals never feel in robust health, they lose energy and brightness, and in time always become victims to fibrositis.

The usual organisms which we have to combat are the *B. tuberculosis*, *B. coli*, staphylococci, gonococcus, and *B. typhosus*. Of these *B. coli*, alone or mixed, is by far the most frequent, streptococcal infection is not very common, and the *B. proteus*, leptothrix, sarcina and yeast are extremely rare. The *B. tuberculosis* I do not propose to consider here as no known urinary antiseptic has any effect upon it.

At the outset we have to make up our minds that we do not as yet possess a perfect urinary antiseptic, nor even a very powerful one, and my object in writing this paper is to try to define more clearly the action and value of those most commonly used and so lead to their more accurate application in individual cases. A reliable and efficient bactericidal drug is especially very much needed for treating children, and to avoid the troublesome and objectionable use of instruments in adults.

Before considering the various substances in detail, I wish

to advert briefly to one method which has sometimes been relied on to determine their efficacy, and which I have found very fallacious as a test, namely, the observation of the time within which ammoniacal decomposition sets in after the urine has been voided.

Ammoniacal Decomposition of the Urine.

In estimating the value of urinary antiseptics weight has sometimes been laid on the length of time the urine resists ammoniacal decomposition after it has been passed. This, however, is a very uncertain criterion and has no definite value in settling the matter, as the following simple observations serve to demonstrate. When samples of urine of ordinary normal acidity are passed into urine glasses which have been sterilised in boiling water and the uncovered glasses, freely exposed to the air, are kept standing on a laboratory table, it is found that very varying times elapse before the different samples become alkaline and ammoniacal with a free growth of organisms in them. In very numerous observations the time was found to vary from two to twenty-nine days, the majority taking roughly about ten to fifteen days, while a few remained acid indefinitely. When the vessels were loosely covered over with paper decomposition was as a rule delayed, and when they were plugged with cotton-wool the urine remained sterile. If the urine glasses were merely rinsed with water or were kept in the hospital test-room decomposition set in more rapidly than when strict cleanliness was observed. The conclusion must be drawn that the onset of decomposition depends on the time and extent to which any particular glass of urine happens to become contaminated by urea-splitting organisms. Cocci grow scantily in acid as compared with alkaline urines, and it is only when alkalinity sets in that a really abundant growth takes place. The ammonium carbonate which the organisms set free from urea has to neutralise the acidity of the urine before this occurs, and it is on this account that strongly acid urines resist ammoniacal decomposition longer than feebly acid or alkaline ones do. It was found, moreover, that highly acid urines often decomposed more quickly than the less acid. There was no regularity in time or in degree of acidity in the matter, and it seemed to depend entirely on the chances of contamination. Urines

which are alkaline when passed resist decomposition for about four days at most. A really powerful urinary antiseptic would of course inhibit bacterial growth in voided urine, but no such substance is yet known, and it was found that the urine of persons taking copaiba, benzoates, salicylates, acid sodium phosphate, and other substances decomposed in the same irregular and uncertain manner as normal urines do and within the same limits of time. This does not necessarily imply that these drugs have no retarding effect on bacterial growth and ammoniacal decomposition in the urine, it simply means that one cannot estimate the value of a comparatively weak urinary antiseptic by observation of the time required for the urine to decompose after it has been passed, which is always very irregular and seems to be largely a matter of chance contamination. Similar observations made with urines kept in an incubator at body temperature gave similar results, and in these to prevent rapid evaporation the urine glasses were loosely covered with watch-glasses.

Acid Sodium Phosphate (NaH_2PO_4).

Since it was first recommended by Hutchison, acid sodium phosphate has been largely used in practice to increase the acidity of the urine. On the ground that it is the natural acidifying agent of the urine, it is very generally assumed that one has only to increase the dose and the urine becomes proportionately more acid. This, however, is far from being the true state of matters. Part of it only, perhaps one-half, becomes absorbed from the bowel, and after this has encountered the alkaline contents of the duodenum and been absorbed into the alkaline blood and subjected to the selective eliminating action of the kidneys, the proportion of it which emerges as the acid phosphate of sodium varies so much that the extent of its influence on the total acidity of the urine is an inconstant and uncertain quantity. In the duodenum and blood more or less of it may be converted into the alkaline di-sodium phosphate (Na_2HPO_4), and this may again be partly dissociated into the acid mono-sodium phosphate (NaH_2PO_4) and so excreted in the urine. The chemical interchange is represented by the equation $Na_2HPO_4 + H_2O \rightleftarrows Na-HO + Na\ H_2PO_4$.

Miss J. Small, Carnegie Research Scholar, made gravimetric determinations of the total P_2O_5 excreted in the urine of a

person on fixed diet who took 120 grains (8 grams) acid sodium phosphate in one day. The average amount of P_2O_5 on the two preceding days was 1·337 grams, on the third day (the day on which the drug was taken) it rose to 3·376 grams, on the fourth day it was 2·406 grams, and on the fifth day 1·686 grams. Thus 51 per cent. of it was absorbed and the remainder excreted in the fæces. The acid phosphate in relation to the alkaline phosphate was exactly doubled in amount during the first twenty-four hours, and by the third day had returned to its previous level.

Under normal conditions of health the hydrogen ion concentration (reaction) of the body fluids is kept remarkably constant, that of the blood being about *p*H 7.4 (faintly alkaline) and of the urine round about *p*H6 (slightly acid), 7 representing neutrality. The possible limits of change in reaction are therefore small, and this is brought about by the "buffer" effect of the sodium bicarbonate, phosphates, amino-acids, proteins, and other substances in the blood-plasma, which greatly slow and discourage chemical action and prevent sudden or extreme changes taking place in its chemical composition. It is necessary for the proper functioning of the body cells that they should be kept bathed in a faintly alkaline medium, and that too high a degree of acidity or alkalinity be prevented. The kidneys play an important part in accomplishing this balance, they actively excrete foreign and excess substances, and they maintain the healthy normal composition and reaction of the blood by eliminating acid bodies and retaining in the blood as much alkali as it requires, their activities in this respect being confined almost entirely to changing the weakly alkaline mixture of phosphate salts in the blood to the more decidedly acid mixture of phosphates in the urine. The relative amounts of the acid mono-sodium phosphate and the alkaline di-sodium phosphate in the blood are constantly, therefore, undergoing modification according to the passing needs of the blood to maintain its normal alkalinity against the intake of acid or alkaline substances, and this in turn is reflected in the relative proportions of these two salts in the urine, and its consequent titrable acidity (with NaOH). Acid phosphate of sodium is a very soluble salt, it is rapidly absorbed and rapidly excreted, hence the effects of its administration or stoppage are very fully apparent in the urine in a few hours. In large doses (half-ounce daily or less) it may cause diarrhœa, and this disturbs the composition of the urine apart from any strictly chemical effect it may exercise. Its purgative action is irregular and probably depends on the extent to which it is converted into the di-sodium phosphate in the upper bowel.

The Action of Urinary Antiseptics

It has to be clearly borne in mind that the "true acidity" or "hydrogen ion concentration" of the urine is a matter quite distinct from its "total acidity." The latter is measured by titrating a small portion of the twenty-four hours' urine with deci-normal NaOH. There are no free acids in normal urine and the NaOH simply determines the quantity of acid phosphates (sodium, calcium, etc.), or other acid salts present, by combining with them and satisfying their chemical affinities. It in no way determines the "true acidity" or "hydrogen ion concentration." This depends on the number of dissociated H ions present in the urine, and the buffering action of the mixture of urinary salts always prevents any very high degree of such dissociation. But it is the number of dissociated or free H ions (the hydrogen ion concentration) which determines the real active acidity of a solution, and the titrable acidity with NaOH gives no information about this.

The true reaction of a solution depends on the relative amounts (or concentration) in it of hydrogen ions ($\overset{+}{H}$) and hydroxyl ions ($O\overset{-}{H}$). When these are equal the solution is neutral, when the $\overset{+}{H}$ ions are in excess it is acid, and when the $O\overset{-}{H}$ ions are in excess it is alkaline. A "strong" acid, such as HCl, is one which dissociates freely in a solution and a "weak" acid, such as H_3PO_4, is one which dissociates feebly, and the same holds true of "strong" and "weak" bases. Even in a watery solution acid sodium phosphate dissociates very slightly, and in a complex buffer mixture like the urine the tendency is still further and greatly reduced. Hence urine never attains a high degree of true acidity by dissociation of its natural acidifying agent, and even when the titrable acidity is greatly raised by giving acid sodium phosphate the real acidity may remain unchanged (*Experiment* IV). It is only free electrically charged ions which are active in determining acidity or alkalinity, undissociated H or OH ions in a solution have no effect.

Hydrogen ion concentration is now for convenience generally expressed as a logarithm pH, pH_7 representing neutrality, under 7 acidity, and over 7 alkalinity. It can be measured by an electrical apparatus which determines the conducting power of the solution, but the ordinary method, which is sufficiently accurate for most purposes, is to use a series of "indicators," each of which changes colour within a narrow range of H ion concentration. All my determinations were made in this latter way. The total acidity was determined by titrating with a deci-normal solution of NaOH, with phenolphthalein as an indicator, using the correction for the varying specific gravities of different samples of urine which was suggested by Joulie and employed by Jordan in his research on urinary antiseptics.

This method gives the titrable acidity in terms of total solids, and not of the bulk of fluid, that is, it eliminates the effect of a dilute or concentrated urine.

1. **Effect of Acid Sodium Phosphate on the Total Acidity of the Urine.**—The usual effect is to raise the total acidity, but always in a varying and irregular degree. Sometimes it may even fall at first, and often in the same individual a large dose has a lesser influence in raising it than a smaller dose.

EXPERIMENT I.

Three healthy men on a nearly uniform diet. The urine of twenty-four hours was collected and its total acidity determined by titration with deci-normal NaOH *and phenolphthalein.*

Day.	I.	II.	III.	
1	3·1	2·3	3·6	No drug.
2	2·8	4·6	1·8	
3	3·4	2·2	2·0	
4	3·9	4·0	2·5	
5	3·4	3·6	2·5	
6	4·0	3·4	2·5	At 12 noon Acid Sod. Phos. 40 gr. six times daily (16 grams).
Average .	3·4	3·3	2·5	
7	4·6	4·0	3·0	
8	6·1	6·1	4·9	
9	5·8	6·6	4·7	
10	6·4	7·2	3·5	
11	5·2	7·3	1·6	Drug stopped at 12 noon.
Average .	5·6	6·2	3·5	
12	4·0	5·7	3·1	
13	2·1	3·7	2·6	
14	3·2	3·9	2·3	
15	3·2	2·5	2·8	
Average .	3·2	3·9	2.7	

There is no fixed proportion, therefore, between the amount taken by the mouth and the degree of titrable acidity of the urine. These points are all clearly brought out in the following observations (*Experiments* I and II). From these it is very evident that as a rule more or less of the acid sodium phosphate is excreted as such, and raises the total acidity of the urine as estimated by titration with an alkali; but the rise is not necessarily in proportion to the quantity taken by the mouth, as the amount in the urine is really determined by the needs of the blood-plasma for the time being.

In *Experiment* II 40 grains six times daily had a greater effect in raising the total acidity than 80 grains six times daily in all three men, and there was no diarrhœa with the larger doses to disturb the result.

EXPERIMENT II.

Three healthy men under the same conditions as in Experiment I.

Day.	I.	II.	III.	
1	4·3	3·1	1·1	No drug.
2	3·2	3·3	5·1	Acid Sod. Phos. 10 gr. thrice daily (2 grams).
3	3·0	2·7	4·2	
4	3·1	2·7	4·2	20 gr. thrice daily (4 grams).
5	3·5	3·5	3·8	
6	5·5	3·5	2·0	
7	5·6	3·6	5·0	40 gr. six times daily (16 grams).
8	5·8	5·0	7·0	
9	5·1	4·2	6·2	
10	5·7	...	4·5	80 gr. six times daily (32 grams).
11	4·3	4·2	3·8	
12	...	2·6	3·1	
13	2·8	4·5	4·7	
14	3·0	3·8	1·8	No drug.
15	4·3	2·7	2·9	
16	3·8	2·4	1·8	
17	3·6	3·8	0·9	

2. **Effect of Acid Sodium Phosphate on the Hydrogen Ion Concentration of the Urine.**—It was found that the administration of acid sodium phosphate by the mouth had practically no effect on the hydrogen ion concentration of twenty-four hours' normal acid urine (*Experiment III*). A large number of observations were made on healthy men with very varying doses; but the result was always the same, and is due to the buffer action of the mixture of salts in the urine. In several cases the total acidity by titration with NaOH and the hydrogen ion concentration (true acidity) were determined simultaneously, and it was found that while the former was augumented the latter remained unaffected (*Experiment IV*).

As a check on these results quantities of $\frac{1}{2}$ to 2 grains of acid phosphate of sodium were added to 1 oz. of fresh normal urine. The total acidity always rose proportionately while the pH remained quite unchanged. When water was used instead of urine, total acidity and pH both showed increased acid values. This demonstrated the powerful buffer effect of the mixture of salts in the urine in inhibiting any marked increase in hydrogen ion concentration. Henderson and

Palmer by giving 10 grams (150 grains) acid sodium phosphate in one dose got a slight rise in the hydrogen ion concentration, but "only slightly greater than that which occurs in normal cases without mono-sodium phosphate intake." It is not practicable, however, to give such large quantities at one dose to patients, and they cannot as a rule be kept up without causing diarrhœa.

EXPERIMENT III.

Two healthy men on a nearly uniform diet. The acidity (pH) was determined by "indicators."

Day.	I. *p*H.	II. *p*H	
1	6·1 No drug	5·5	No drug.
2	6·1	5·4	
3	6·3	5·7	
4	6·1	5·5	Average 5·5.
5	5·0	5·7	Acid Sod. Phos. 20 gr. thrice daily (4 grams).
Average .	5·9		
6	Acid Sod. Phos. 10 gr. thrice daily (2 grams)	6·5	Average 6·1.
7	6·2	5·8	40 gr. thrice daily (8 grams).
8	5·4	5·4	
9	5·4	5·5	
10	5·9	5·1	
11	6·2	5·4	Average 5·4.
12	6·1	5·8	40 gr. six times daily (16 grams).
13	6·4	5·6	
14	6·2	5·8	Average 5·4.
Average .	5·9		

EXPERIMENT IV.

Healthy man on nearly uniform diet.

Day.	*p*H.	Total Acidity by NaOH.	
1	6·1	4·1	No drug.
2	6·3	5·6	
3	6·4	3·5	
4	6·1	4·8	
5	6·1	4·2	Acid Sod. Phos. 40 gr. thrice daily (8 grams).
6	6·1	7·6	
7	6·1	8·9	
8	6·1	3·5	No drug.
9	6·3	3·4	
10	6·6	1·8	
11	6·7	0·76	
12	6·6	1·8	

Clinical Uses.—In cases which show a persistent mild alkaline reaction of the urine and consequent precipitation of earthy phosphates and carbonates within the urinary passages, the administration of acid sodium phosphate gets rid of the condition by providing an acid salt which can combine with and neutralise the excess of alkali. The deposit of earthy salts and possible formation of calculi can thus be guarded against. Enough should be given to produce distinct acidity of the urine to litmus paper.

It may also be given with great advantage when *slight* ammoniacal decomposition is going on in the bladder from bacterial infection. In acid urine the micrococcus ureæ and other ammonia-forming organisms grow with difficulty until they succeed in turning the urine ammoniacal, when they at once begin to flourish much more luxuriantly, or expressed otherwise, it is well recognised that acid urines do not putrefy so readily as alkaline ones. The acid phosphate combines with the ammonia to form sodium-ammonium phosphate, and if in sufficient amount may thus succeed in keeping the urine acid and lessening the tendency to its decomposition from bacterial growth. Its action can be greatly supplemented by hexamine or boric acid. In very ammoniacal urines its action in this direction is not effective, as it is never in sufficient quantity to neutralise all the free ammonia present, and the urine remains ammoniacal. Boric acid or ammonium benzoate should be given in addition, as hexamine has no action so long as the urine remains alkaline. If the sepsis still persists the bladder should be washed out regularly with boric lotion to lessen the ammonia, bacteria, and pus, and so give the acid phosphate whatever chance it may have to overcome the alkalinity of the urine. Before and after operations on the urinary passages it may be given to maintain the total acidity of the urine and thus discourage bacterial growth in it.

At the present time it is perhaps most frequently prescribed along with hexamine under the idea that by increasing the total acidity of the urine the hexamine splits off a larger amount of formaldehyde than it would otherwise do. If the urine is slightly alkaline or of low acidity this does happen, provided it succeeds in turning the urine distinctly acid. But when the urine is already markedly acid the administration of acid sodium phosphate has no effect in increasing its hydrogen ion concentration, owing to the complete buffering action of the

complex mixture of salts present in it. Hence with a urine already frankly acid to litmus it is unnecessary to give it along with hexamine. As long as the urine keeps definitely on the acid side of pH_7 it splits off formaldehyde from hexamine, and at the same time neutralises the ammonia which is also given off in the process, and the administration of more acid sodium phosphate may not be required to increase the activity of the urine in these respects. Nevertheless, in order to neutralise the "alkaline tide" after meals and to keep the urine on the safe side as regards acidity, it is usually good practice to give it along with hexamine in these circumstances.

In cases of *B. coli* cystitis with an acid reaction of the urine to litmus and pus present, it is often impossible to increase the total acidity of the urine by giving acid sodium phosphate. The following case serves as an illustration of this. The explanation must lie in the occurrence of obscure chemical changes which are difficult to follow out and explain.

Woman, 45.—*Urine acid to litmus and containing coliform organisms and much pus. Has been taking* 10 *grains hexamine thrice daily and there is a marked formaldehyde reaction in the urine.*

Day.	Total Acidity by NaOH.	
1	2·3	
3	2·5	
6	1·7	
11	1·5	
12	...	Acid Sod. Phos. 20 gr. thrice daily.
14	2·0	
17	1·5	
19	3·1	40 gr. thrice daily.
21	2·0	
25	2·2	
27	2·4	
31	2·0	
33	1·7	
34	4·5	80 gr. six times daily.
36	2·2	
37	1·0	
38	1·7	

Even in cases where the urine is faintly alkaline or neutral I have also sometimes found it impossible to raise the total acidity by giving ordinary doses (40 grains four times daily) of acid phosphate of sodium.

The Action of Urinary Antiseptics

Benzoic Acid and Benzoates.

It has been recognised since the time of Berzelius (1813) that the ordinary mineral and vegetable acids do not neutralise or make acid an alkaline urine, a finding which was confirmed by Magendie in 1818 and by Woehler in 1824, the explanation in the case of the mineral acids being that flesh-eating animals can always furnish abundance of ammonia to combine with them, and thus protect the alkali of the blood and prevent it being drawn upon and dangerously diminished. The mineral acids are therefore excreted in the urine as neutral salts of ammonium or other alkalies, and in consequence do not increase its acidity. In the case of the common vegetable acids (acetic, tartaric, citric) and their salts, Gilbert Blane pointed out in 1808 that potassium acetate or citrate alkalinise the urine as effectually as the corresponding carbonate or bicarbonate, and in 1824 Woehler showed that they are oxidised in the body and excreted as alkaline carbonates and thus act as alkalinisers of the urine. Benzoic acid (C_6H_5COOH) and benzoates, on the other hand, are capable of acidifying a neutral or alkaline urine, and they do this in virtue of the benzoic acid being synthesised in the kidney to hippuric acid which takes up alkali and is excreted in the urine as a hippurate. This was first observed by Alex. Ure in 1841. Shortly afterwards Dessaignes showed that the hippuric acid is formed by the combination of benzoic acid with glycocoll, and in 1877 Bunge and Schmiedeberg proved experimentally that the synthesis takes place in the kidney. Alex. Ure was also the first to use benzoic acid for the purpose of rendering alkaline urines acid and of preventing the deposit of earthy phosphates, and he recognised that it "solved the hitherto embarrassing problem of making an alkaline urine acid," remarking at the same time that it is always easy to make an acid urine alkaline. Following him Walker reported four cases of *dysuria senilis* with ammoniacal urine in which an emulsion of benzoic acid and copaiba cleared up the urine successfully. Later (1874) Gosselin and Robin, using benzoic acid and ammonium or sodium benzoate, emphasised their value in a series of cases of ammoniacal cystitis, stating that the urine became acid or neutral in five to nineteen days, and that the amounts of pus, blood, and phosphatic deposit were greatly diminished. They also advised that a course of such treatment should be given previous to any operative interference in these cases.

When ammonium benzoate is taken by healthy men in 20-grain doses thrice daily, I find that little or none of the benzoic acid escapes conversion into hippuric acid of which it will yield nearly 90 grains in the urine, and its excretion begins in about half an hour or even less. The ammonium part of it is converted into urea in the body, and thus has no effect in increasing the alkalinity of the urine, while the benzoic or hippuric half is left free to combine with alkali which it carries out of the body through the kidneys. The hippuric acid is thus excreted not as the uncombined acid but as an alkali salt—a hippurate—neutral in reaction, and therefore incapable of any direct effect in increasing the acidity of the urine. It has, however, a marked indirect effect by taking up so much alkali that the relative proportions of the alkaline Na_2HPO_4 and the acid NaH_2PO_4 are altered in favour of the latter, thus increasing the urinary acidity. Miss Small determined for me the amount of P_2O_5 in the urine of a person on fixed diet before and after taking 60 grains daily (4 grams) ammonium benzoate for two days. The normal average amount was 1·1317 grams per day, and on taking the drug it rose to 1·5995 grams, 1·542 grams, and 1·645 grams, while the proportions of acid to alkaline phosphate was also considerably increased. In this way doses of 60 to 75 grains of ammonium benzoate per day ensure a higher titrable acidity of the urine (due to NaH_2PO_4), which therefore does not readily become ammoniacal; but organisms grow in it after voiding as freely at least as they grow in other acid urines, and the degree of acidity never exceeds that of normal acid urines. It therefore confers little or no antiseptic action on the urine beyond what is attributable to the acidity. As long ago as 1858, Kerner noticed that the administration of benzoic acid did not raise the acidity beyond normal limits, and Johnston found that in persons with normally acid urines ammonium benzoate was also ineffective in doing so, but that when the urine was weakly acid or alkaline in reaction it then raised the total acid output. He also found that in no case, whether the urine was alkaline or acid, did it raise the pH acidity beyond the ordinary limits of normal acid urine. Any increase of urinary acidity which it may bring about is, therefore, not a direct matter of the presence of benzoic or hippuric acid, but of acid sodium phosphate. Hippuric acid and alkaline hippurates are practically inert substances. They have no action on the common septic microbes or on yeast, but in an

alkaline or putrefying ammoniacal urine the hippuric acid is split up by the same organisms which decompose urea (van Tieghem) and again yields benzoate which has a slight antiseptic action. Johnston has also shown that with the continuous administration of ammonium benzoate a small amount of unconjugated benzoic acid begins to appear in the urine (as a benzoate) and according to his experimental results this is capable of exercising a certain slight inhibitory effect on the growth of *B. coli*, but not of strepto- or staphylococci. The outstanding action of ammonium benzoate, however, lies in its power of acidifying an alkaline urine by determining an increase in the amount of acid sodium phosphate.

Clinical Uses.—The therapeutical value of benzoic acid and benzoates as urinary antiseptics only comes into play when the urine is weakly acid or alkaline, and more especially when it is septic and ammoniacal. If by their administration the urine can be rendered acid in reaction septic bacterial growth and activity are at once lessened, the ammonia split off from urea by microbic action combines with the acid salts present, and the acid urine secreted by the kidney is then no longer neutralised by the ammonia in the bladder and recovers its normal acid reaction. As soon as this occurs the earthy phosphates cease to be precipitated, pus and mucus and epithelial debris gradually diminish in amount as the bacterial activity lessens, and the urine becomes clear or at least much clearer. In some cases the result is entirely successful, in most only partially so. As long as the urine remains alkaline acid sodium phosphate or boric acid may be given to assist the action of the benzoate, and once the urine is frankly acid hexamine may be also given. In cases of slightly alkaline urine with phosphaturia ammonium benzoate usually clears up the urine in a short time, and may thus prevent the formation of phosphatic calculi.

In *B. coli* infection the urine is almost invariably acid in reaction, and ammonium benzoate is incapable of raising its acidity to a degree which is inhibitory to the growth of coliform organisms; but according to Johnston the unconjugated benzoate which is usually present does exercise a very slight inhibitory effect on the organisms. On the whole, however, it is probable that benzoates have little effect in getting rid of a *B. coli* infection.

Clinical experience has shown that benzoates are of no value in typhoid, tubercle, or gonococcus infections. They can

also have little effect in pyelitis as they traverse the pelvis of the kidney chiefly as inert hippurates.

When it is desired to render an alkaline urine acid ammonium benzoate is a better salt to use than sodium benzoate. A much smaller amount is required as the ammonium ion is converted into urea by the liver, leaving the benzoic acid free to form new sodium or potassium salts and this, by diminishing the alkalinity of the blood-plasma, encourages the excretion from it of the acid sodium phosphate in order to maintain its normal degree of alkaline reaction. With sodium benzoate, on the other hand, a considerable amount of alkali is introduced into the body, and in order to neutralise it the acid substances present in the blood are drawn upon and diminished. Nevertheless, large doses of sodium benzoate are very effectual in acidifying the urine and are almost non-toxic.

Salicylic Acid and Salicylates.

Salicylates are sometimes mentioned in text-books as exerting an antiseptic action in the urine, but in actual practice they are very little used for this purpose. Their effect is similar to that of benzoates, namely, by withdrawing alkali from the blood they tend to increase the proportion of acid salts in the urine and thus maintain or heighten its acidity. Salicylic acid ($C_6H_4 \cdot COOH \cdot OH$) is dealt with in the body in the same way that benzoic acid is, the greater part of it becoming conjugated with glycocoll to form salicyluric acid which, like hippuric acid, is an almost inert and non-poisonous substance (Stockman). A varying amount——usually quite small—is excreted as sodium salicylate, but in such dilution that it cannot be at all effective against the bacteria of putrefaction, and in any case sodium salicylate is a feeble antiseptic. Salicylic acid on the other hand is powerfully antiseptic, but is never found free in the urine. If added to urine it can be readily washed out again with chloroform; but in persons taking up to 180 grains of sodium salicylate per day and with urines of high acidity no free salicylic acid, or only a doubtful trace, was ever obtained, and even when it was given with large doses of acid sodium phosphate the result was always the same.

As sodium salicylate is excreted as an alkaline salicylurate or partially unchanged it does not directly increase the titrable

acidity of the urine (with NaOH). Very many observations of this kind were made on persons taking ordinary doses, but there was never any *abnormal* increase in the total acidity. After the conjugation of salicylic acid with glycocoll the salicyluric acid so formed requires alkali, which it withdraws from the blood, and this tends to render the urine more acid. As is well known very large doses of salicylic compounds may thus produce acidæmia with grave or even fatal results, and with the typical symptoms of acidosis.

B. coli and staphylococci grew quite well when inoculated into tubes containing urine from patients who were receiving large doses of sodium salicylate, and there is no reason to think that such urine has much, if any, restraining influence on their growth. Some strains of streptococci also grew quite well, while others seemed to be considerably inhibited.

SALOL appears in the urine as sodium salicylurate and sodium sulphocarbolate, both of which are substances of negligible antiseptic power, in addition to which they can be present with ordinary dosage only in very small quantity and in very diluted form. It is difficult to understand how salol ever came to have any great clinical reputation as a urinary antiseptic.

No therapeutical investigations have ever been made with AMMONIUM SALICYLATE for the purpose of comparing its action with that of ammonium benzoate on putrefying urines, nor is it known whether in such urines salicylic acid is regenerated from salicyluric acid as benzoic acid is from hippuric. Further, salicylic compounds are much more toxic than benzoic, and hence in urinary cases it is preferable to use the latter as is the custom in practice.

Boric Acid.

Boric acid is a very weak acid and a feeble antiseptic, but clinically it is extremely useful and of great practical value in the treatment of certain urinary infections. It is eliminated by the kidneys probably as the metaborate ($NaBO_3$) or pyroborate ($Na_2B_4O_7$) of sodium or other alkali. Its action is exerted irrespective of whether the urine is acid or alkaline, and this is often a great advantage and of especial utility in cases in which it is found impossible or undesirable to maintain an acid reaction.

Clinical Uses.—In the acute *B. coli* pyelitis of children and adults, and in acute cystitis, it may be given along with the

usual alkaline treatment from the very beginning, and adds a valuable antiseptic element to the merely symptomatic effects of the alkalis. In staphylococcic and chronic *B. coli* infections and in ammoniacal cystitis it often acts as well as reputedly more powerful remedies, and it can if necessary be combined with these. At the same time it may be used as a lotion to wash out the bladder.

In treating acute cases of pyelitis and cystitis with alkalis it is often difficult to maintain a steady alkaline reaction of the urine, and in adults 150 grains (10 grams), or a good deal more, of sodium or potassium citrate in twenty-four hours may be requisite. Sodium bicarbonate, which is a more rapid and effective alkaliniser of the urine, may be given separately and in addition, to an amount which serves to keep the urine alkaline to litmus paper. The advantage of using the two alkaline salts simultaneously lies in the risk of disturbing gastric digestion by the continued administration of large doses of the bicarbonate, whereas potassium citrate is a neutral salt only converted into the carbonate after it reaches the blood. Even when extreme doses of alkali are given the *p*H of the urine does not go much beyond 8 on the alkaline side, and after some days always tends to decrease, as if some adjustment were being effected by the body against the large intake of alkali.

The ordinary dosage of boric acid is 10 to 15 grains three or four times daily. Ten grains hardly dissolves in half an ounce of water, but almost does so with the help of a drachm of glycerin. Sodium or potassium citrate also increases its solubility so that boric acid 10 grains, potassium citrate 20 grains, and water to ½ oz. make a perfectly clear solution, and if a larger dose of boric acid is desired it can be dissolved up by including enough glycerin in the prescription. Similar mixtures with potassium acetate give a precipitate. Boric acid 10 grains, ammonium benzoate 20 grains, and water to ½ oz. also form a perfectly clear solution, and the combination is a very useful one when the urine is alkaline and infected. Hexamine (10 grains) can be added to it, and although the solution is an acid one and sets free a certain amount of formaldehyde, the amount is so small that it is negligible as regards any stomach disturbance. If the urine is alkaline it is useless to add the hexamine, but given an acid urine the combination of these three substances is the most powerful urinary antiseptic I know.

The Action of Urinary Antiseptics

The urine of persons taking 10 to 15 grain doses of boric acid thrice daily shows no change in its titrable acidity beyond the normal variations, and also no increase in its pH value as it is a very weak acid and dissociates very feebly in solutions. The action must therefore depend on the somewhat weak antiseptic effects of the borates present, and is merely inhibitory to the growth and vitality of the bacteria. As a set-off to this the borates probably do not lessen the defensive and recuperative powers of the leucocytes and tissues generally, which may thus be left in a better position to deal with the invading organisms.

Boric acid in repeated small doses used as a food preservative has acquired the reputation of being highly injurious. It is said to cause irritation of the intestine, skin eruptions and falling out of hair, nephritis, and malnutrition. In giving it, often for weeks at a time, to patients with *B. coli* infection of the bladder, I have never met with any of these injurious effects.

Hexamine.

The mode of action of hexamine and its clinical value and limitations are now so well understood and appreciated that a mere re-statement of the chief points is all that is necessary here. It is a white crystalline substance very soluble in water and is made by the interaction of ammonia and formic aldehyde. In acid solutions it at once begins to decompose again,

$$N_4 (CH_2)_6 + 6H_2O = 4\ NH_3 + 6\ CHOH,$$

and its action as a urinary antiseptic depends on this liberation of free formaldehyde. In alkaline solutions no decomposition takes place. Hexamine is non-toxic, it is rapidly absorbed, circulates in the blood unchanged, begins to be excreted in the urine in about twenty minutes, and reaches its maximum amount there in about four hours or more. It is only when it comes into contact with acid urine in the kidneys and bladder that any formaldehyde is set free, and in a weakly acid solution such as the urine this usually occurs slowly and to a comparatively limited extent. With a dosage of 40 grains daily it is present in the twenty-four hours' urine (say) as about 1 in 500 parts; but the amount of formaldehyde split off in the bladder has never been estimated higher than 1 in 5000 parts of urine, and ordinarily is certainly very much less than this.

The amount varies greatly with different urines, most probably according to their hydrogen ion concentration, and this constitutes an element of uncertainty in treatment. With full doses hexamine is always abundantly excreted in the urine, the trouble being that it does not split off formaldehyde in sufficient amount, and if the urine is already definitely acid the administration of acid sodium phosphate in ordinary doses does not materially, if at all, increase the true acidity and therefore does not lead to a greater production of formaldehyde. When there is pus, epithelial cells, and mucus, these combine with and fix the formaldehyde and thus lessen the amount in solution.

Clinical Uses.—A strength of 1 in 5000 is not strong enough to be bactericidal (except perhaps in the case of *B. typhosus*), but very much weaker dilutions are very inhibitory to the growth and vitality of *B. coli*, staphylococci, and streptococci, while the gonococcus and tubercle bacillus seem to be quite unaffected. It is useless to give it as long as the reaction of the urine is alkaline to litmus, and unless the urine can be previously made acid with acid sodium phosphate, ammonium benzoate, boric acid, or a combination of these. An effective dose is 10 to 15 grains three or four times daily, and added to this there must be a frankly acid reaction of the urine as formaldehyde is liberated by all urines which show a hydrogen ion concentration well on the acid side of pH_7, which is tantamount to a distinctly acid litmus reaction. It is always well to make sure that free formaldehyde is present, and the most convenient test for this is to add to the urine in a test tube a few drops of a 1 per cent. solution of phloroglucin followed by a few drops of a 30 per cent. solution of sodium hydrate, when a deep cherry-red colour develops.

Some cases of coliform and staphylococcic infection clear up very satisfactorily with hexamine; but persistent treatment for months is often necessary to wear down the vitality of the bacteria, so that the natural defensive powers of the tissues can ultimately deal with and exterminate them. The bladder symptoms subside very rapidly in most cases and this is apt to lead to a want of persistency in treatment.

Hexamine decomposes so gradually that as a rule very little formaldehyde is set free in the kidney, and hence it is of only moderate value in treating pyelitis.

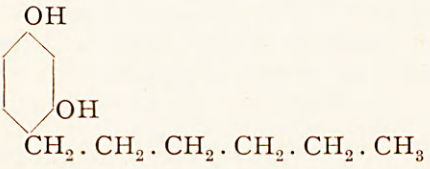
When it is prescribed in mixture with acid sodium phosphate formaldehyde is set free, but never in sufficient amount to

disturb the stomach if the mixture is to be finished in a few days. It is customary, however, to dispense them in separate bottles.

Cases have been recorded in which it has caused renal irritation and bleeding, and more frequently strangury, pain, and irritation in the bladder. The former must be very rare and so is strangury, for after much experience in giving hexamine I have never seen either occur, although some irritation of the bladder is not so uncommon. Such symptoms subside rapidly if the urine is made alkaline with sodium bicarbonate. I have tried washing out the bladder with solutions of formaldehyde 1 in 3000 to 1 in 5000, but they always caused a great deal of local irritation and had to be given up.

Hexyl-resorcinol.

In the course of a research designed to discover an ideal internal antiseptic Johnson prepared this substance, and on examination it was found to be non-toxic to man in therapeutical doses and to render the voided urine highly bactericidal *in vitro*. It is the hexyl alkyl derivative of resorcin ($C_6H_3(OH)_2C_6H_{13}$)



and is a white wax-like solid insoluble in water but soluble in olive oil. It is stated to be 46 times more potent than phenol as a germicide and 150 times more than resorcin, and "is believed to be one of the most powerful organic germicides ever described." Unfortunately it is detoxicated in the body by being conjugated previous to its excretion in the urine and the conjugated compound is inert. A small portion of it seems usually to escape detoxication, and it is this portion, irregular in amount both in the same and different individuals and at different times, which is effective against bacteria in the urinary passages. It has the great advantage of being active in urine of either acid or alkaline reaction, but curiously enough if sodium bicarbonate be given at the same time the urine is deprived of bactericidal powers. No satisfactory

explanation of this is meantime forthcoming, but it has been ascribed to change in the surface-tension of the urine. In 1924 Leonard published two papers describing its action on man and animals and detailing its effects in cases of urinary infection with *B. coli* and various cocci. From these it appears to be very active against the latter but not so satisfactory against the former. Judging from only a moderate amount of experience of it in *B. coli* infections and in mild cases of staphylococcic infection with alkaline urine, I cannot say the results have been better than those obtained with other urinary antiseptics. It reduces the number of organisms and relieves symptoms promptly enough, but is not specially effective in eradicating the infection. I have not had a good opportunity of testing its efficacy in a severe case of ammoniacal cystitis.

It is given in gelatin capsules containing 0·15 gram dissolved in olive oil, two to four capsules thrice daily after food, or in a $2\frac{1}{2}$ per cent. solution in olive oil of which a teaspoonful constitutes a dose (equal to 0·1 gram). It is irritating to the stomach and is therefore best given after food, and the larger doses are apt to cause catharsis which usually, however, ceases after a day or two. Its relative clinical value can only be determined after a much longer and more general trial than it has as yet had. Although it emanates from research work in a medical school, it is the subject of a patent both in the United States and in this country.

Methylene Blue—Acriflavine.

I have used METHYLENE BLUE occasionally for many years past in treating cases of *B. coli* cystitis in doses of 2 grains (in pill) three or four times daily. It colours the urine blue which is an objection to its use. Its action is quite definite and comparable to that of hexamine. The organisms and the pus and the subjective symptoms usually diminish very markedly in a few days, but the infection persists.

ACRIFLAVINE is stated by Browning and Gulbransen to have the very unusual property of being more active as a bactericide in serum solutions than in water. It is excreted in the urine to which it imparts a deep yellow colour and marked bactericidal properties *in vitro*, and they suggest that it may prove of value in combating infections of the kidney

and urinary passages. It was given in a dose of 1½ grains (0·1 gram) thrice daily in keratin capsules, and the necessity of administering it in this way proved to be a serious practical drawback. If the capsules were not sufficiently coated they burst in the stomach and caused severe and sometimes prolonged sickness, and if too thickly coated they were apt to pass through the intestine unchanged. With care, however, these drawbacks can be avoided and the urine kept of a deep yellow colour. The urine did not prove to have any marked bactericidal properties in cases of *B. coli* and mild septic infections, and there took place merely a certain amount of inhibition of the bacterial growth. Acriflavine is much more active as a bactericide in alkaline than in acid media outside the body, but in several cases of *B. coli* cystitis I have kept the urine alkaline for weeks at a time while acriflavine was being given, without perceptibly increasing its therapeutical effects.

Copaiba—Oil of Sandal Wood.

Observations were made clinically with the Resin of Copaiba and with the essential Oil of Copaiba. Both were prepared specially pure.

The RESIN was given as an emulsion in 30 gr. doses thrice daily (6 grams). It did not impart to the urine the well-known copaiba odour, nor did it appear to produce any local or systemic effects. The urine exposed to the air putrefied in the same varying times as normal urines, and *B. coli*, staphylococci, and streptococci when inoculated into test-tubes containing it grew very well. It is excreted abundantly in the urine, which with strong H_2SO_4 gives a deep red colour, and with HNO_3 a precipitate resembling albumen but soluble in alcohol. In a case of gonorrhœa it had no apparent action in checking the discharge.

OIL OF COPAIBA was given in 15 minim doses three, four, and six times daily. The urine always had a characteristic odour, and gave a deep red colour with H_2SO_4 but no precipitate with HNO_3. It is said to be excreted in the urine partly in combination with glycuronic acid and partly unchanged. The voided urine became ammoniacal within normal limits of time, and in test-tube experiments with *B. coli*, streptococci, and staphylococci there seemed to be no hindrance to their growth. Test-tube experiments of

this kind cannot, however, be taken as an exact criterion of what happens in the body, because many cases of *B. coli* cystitis when treated with oil of copaiba and with oil of sandal-wood showed at once marked improvement in symptoms and a diminution in the number of organisms. The organisms never entirely disappeared, however. In gonorrhœa and gonorrhœal cystitis the action of large doses (60 to 90 minims per day) was very marked. With our present knowledge we can only conclude that the action of these essential oils is a selective one on the gonococcus, and one which is not shared by any of the other ordinarily used urinary antiseptics.

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