THE USE OF QUININE IN NORMAL LABOUR.

BY

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THERE may, even yet, be purists or idealists who will quarrel with the title of this paper. I have a keen recollection of entering a vicarage at 6 p.m. one day, persuading the hostess of a tea party to retire (most reluctantly) to an upper room, and being able to congratulate her on the birth of her eldest daughter while yet the vicar was speeding the parting guests at 6.20 p.m. This is the ideal of midwifery at which we should aim; but, unfortunately, it is very rarely realized, and there are few of us who would not, if we could, fortify the parturient woman against the possible dangers of her labour.

About five years ago I brought before the Clinical Society of Bath a method of pre-natal quininization which owed its origin to Dr. Philip Jones of Coleford. At that time our claims for the method were very modest. They were, roughly, that labour was considerably hastened; that it was rendered easier; and that the general well-being of the patients was improved. Since that time a large number of cases have been given this routine, and something over 400 of them have been under the direct observation of Dr. Jones and myself. In all, the method has been on trial for seven years, and, so far from modifying the claims of five years ago, further experience has made it necessary to add to them.

This progress has led me to a careful study of quinine—the drug—and has brought to my notice the experiences of various workers who have studied the action of quinine in every stage of pregnancy. Such a study would tend to make one very critical of any claim made for this routine; but, rather to my own surprise, this study of the drug—in my own case—appeared to intensify the logic of such conclusions as have been brought forward. I propose, therefore, to mention a few of the more important points noted in the study of quinine in pregnancy, as opposed to labour.

Perhaps it should be mentioned, first, that the actions of quinine as (1) an external antiseptic, (2) a stomachic, (3) a tonic, and (4) an antipyretic, are generally accepted in practically all textbooks on therapeutics. Even its action in increasing the contractions of the uterine muscle—in the pregnant state or otherwise—is readily admitted. The important point in this connexion is, however, that the circular fibres of the lower uterine segment and cervix take part in this contraction, in direct contrast to the relaxation which they undergo in labour and, to a lesser extent, in abortion.

It is the workers in tropical areas who have taught us that quinine, when used in pregnancy complicated by malaria, is almost a specific to prevent abortion in these cases. Maplestone,¹ in 1927, collected a large series of cases reported by various tropical workers, in which large doses of quinine were given for malaria during pregnancy, with an extremely low percentage of subsequent abortions, and contrasted these results with the high percentage of abortions due to malaria where quinine was withheld. Included among these cases were examples of women who took as much as 100 grains repeatedly, either in error or deliberately, without interfering with the pregnancy. Summarizing these records Maplestone says:

"It seems safe to conclude that quinine in therapeutic doses has no effect in terminating pregnancy, and has rather the opposite tendency by curing the malaria which is the real cause of abortion in these cases."

I think that one warning note must be sounded in reference to these conclusions. We all know, only too well, the type of patient, probably with an imperfectly developed uterus, in whom repeated abortion is only too prone to occur. It is more than probable that in such a case any increase in the normal uterine contractions, such as that produced by even medicinal doses of quinine, might turn

the scale in favour of abortion. In spite of this failure of quinine to determine abortion in these malarious cases the drug has been shown to have great value in "inevitable abortion"—that is, when once the circular fibres of the lower uterine segment and cervix have relaxed—and Kessler,² in Kiel University, and others have quoted large series of cases in which (apart from severe hæmorrhage) quinine has proved greatly superior to operative intervention in the treatment of this condition.

Then, apart from the question of early pregnancy, quinine has been frequently used for the purposes of either bringing on labour or, alternatively, increasing labour pains. In 1907 Conitzer³ gave an account of fifty cases in which quinine was used for increasing labour pains. It was not effective in every case, but when it did act the pains became stronger, of longer duration, and more frequent. In some cases a regular storm of pains came on without injury to mother or child. Conitzer thought that quinine was not indicated in prolonged labour with an undilated os; but he thought that its use at the beginning of labour would often make forceps unnecessary. The same idea is obvious in many of our own textbooks, and it is extended to cover the probability of quinine increasing the patient's resistance to infection.

Haig Ferguson,⁴ in 1921, pointed out the tonic effect upon the uterus of small doses of quinine given for two or three days preceding labour, and further suggested that the increased resistance to infection thus acquired was a good preparation for possible contingencies in the way of "interference." Unfortunately, he did not tell us how to estimate, with any degree of accuracy, the exact date labour would set in. The method of inducing labour by castor oil and quinine has many potent factors other than the quinine, and has, even then, been notoriously unsuccessful unless the patient is close to full term, or unless pituitrin is added. So far from negating the investigations previously quoted, it undoubtedly supports them, and emphasizes the fact that quinine has no effect in initiating labour unless the cervix is already relaxed.

The Puerperium.

Before detailing the actual method and its results, I wish to draw attention to the results obtained by the administration of quinine in puerperal fever. For very many years it has been the most effective drug known to influence this serious infection, and very many successes have been recorded to its credit. In 1923 Gordon Luker⁵ described his method of intramuscular injections of the acid hydrochloride, combined with antistreptococcal serum, and produced almost startling—though limited—figures of recovery rate. Most authorities are agreed that the potent factor in these results was the quinine, though, unfortunately, Luker's results have not been properly confirmed. Green-Armitage⁶ comments very favourably on the method from his Calcutta experiences, and I personally have been impressed by the results I have seen in 12 consecutive cases. It was noticeable in those cases which did well that the large subinvolved—or rather, non-involute⁷—uterus contracted down very rapidly, again demonstrating the power of this drug to influence the uterine muscle even in the most unfavourable circumstances.

The Use of Quinine in Normal Labour.

Dr. Philip Jones commenced his method of quininization in preparation for labour in the spring of 1922, and passed it on to me rather more than a year later. About eighteen months later still the method was outlined in my M.D. thesis, and also brought before the Clinical Society of Bath. Nearly three years later, in 1927, Dr. W. M. Hewetson⁷ of Rhodesia described a very similar routine which he was using for malarious patients, and which had so impressed him in the matter of the ease and rapidity of labour, and in the apparent prophylaxis of febrile complications, that he had come to use it in all cases, whether malarial or not. It was in reply to his letter in the *British Medical Journal* that I first widened our original claims for the method by noting the following points: (1) The general health of patients is improved. (2) Labour is made easier and shorter. (3) Uterine retraction is

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uniformly good. (4) There is no increased tendency to premature labour, precipitate labour, retained placenta, perineal laceration, or "after pains."

The method consists in the administration of a small dose of quinine for three weeks prior to the expected date of labour. It is probable that many prescriptions, containing different salts of quinine, would do equally well. There must, however, be an optimum dose, which is probably equivalent to four or five grains of the sulphate daily. The prescription I have used personally is as follows:

Quin. sulph.	1½ grains
Ac. nitrohydrochlor. dil.	3 min.
Syr. aurant.	½ dr.
Aq.	ad 2 dr.

Mitte 8 oz. Sig. 2 dr. ex. aq. t.d.s. a.c.

It is obvious that with this prescription two bottles will carry the patient over the three weeks, and, keeping in mind the fact that we are for the moment discussing straightforward cases, in which both breech and occipito-posterior presentations are included, we can say that no contraindications have so far been found in over 400 cases. A very few cases were met with in which the patient complained of cramp-like abdominal pains on starting the medicine. In these cases the dose was reduced to half, and most of them returned to the full dose in a few days.

Apart from contraindications, certain points require mention. First, ante-natal work is insisted upon. Secondly, some modification of normal routine is necessary. In the early days of this routine we were not infrequently surprised—and perhaps annoyed—at the number of cases born before our arrival. The point is that the nurse in charge did not send early enough, because she did not realize the rapid, and sometimes easy, progress of some of these cases. In spite of this circumstance, laceration of the perineum was not of more frequent occurrence. I do not think this surprising, because it seems more likely to occur when the patient has to use all her accessory muscles, aided, perhaps, by fundal pressure by the doctor or nurse, than when the uterus is quite equal to the task, and the attendant has only to use restraining pressure to the crowning head.

If this increased rapidity and ease of labour should ultimately gain general acceptance, it seems almost unnecessary to point out that there would automatically be a reduction of forceps cases, and this was a definite feature of my own cases. This point should make a strong appeal to those who hold that "interference" is the dominant factor in puerperal sepsis.

Now, in spite of careful ante-natal work, difficulties must sometimes occur. Occipito-posterior cases will occasionally rotate backwards instead of forwards, and yet I have seen quite a number of these cases rotate forwards and deliver themselves naturally in rapid, though not precipitate, time. Breech cases can be very difficult. Owing to an unfortunate early experience of seeing a series of very large breech babies with extended legs, I have made it a rule to try to turn by external version in the last two or three weeks every breech presentation that comes my way. On the other hand, Dr. Jones, in his series of quinized cases, had seven breeches, all easy, all fairly rapid, and with no foetal mortality.

In order to have some idea of the duration of labour, and to compare the time with that of patients not under quinine treatment, I have taken the time in many cases from the onset of true pains to the birth of the child. To try to stabilize the onset of true pains, I have defined it as the moment when the patient has to stop walking and hold on to the chair or bedpost until the pain passes off. Taking this definition, and excluding difficulties such as persistent occipito-posterior cases, or slight disproportion (even in spite of ante-natal care), the duration of labour appeared to average about six hours for primiparae and three hours for multiparae. I must remind you again that these were "straightforward cases," but even then these times are a great deal shorter than the textbook averages—about sixteen hours for primiparae and eight for multiparae—and probably dependent to some extent upon the definition of "true pains."

Now I wish to make a special point of the fact that "uterine retraction" was uniformly good. This was so marked that I personally have given up the use of ergot or pituitrin as a routine after delivery of the placenta. The maternity sister in one hospital where I was working noted the fact that clots were very rarely seen in these quinized cases in the twenty-four hours following labour, whereas they occurred frequently in other cases. This I consider to be a tribute to the very efficient retraction which obtains with the method. A further point is obvious—namely, if retraction is good involution will also be good. It might, perhaps, be suggested that there is a possibility of superinvolution and consequent sterility, but this was completely negated by seeing a number of cases through two or three or even more pregnancies.

It is, perhaps, permissible to reflect upon the possibilities of this efficient involution as a measure of "prophylactic gynaecology." When we think of the large number of hysterectomies performed at or near the menopause, for haemorrhage due to hypertrophic endometritis and fibrosis uteri—the former almost certainly, and the latter probably, due to chronic subinvolution—the point demands consideration. And, moreover, hysterectomy is not always the greatest trouble that these patients have to face.

Abnormal Labour.

Now it has become necessary to consider certain questions of abnormal labour, because, as is quite obvious, the quality of the uterine contractions can easily make all the difference between the normal and abnormal.

It has already been mentioned that, in this discussion, breech and occipito-posterior presentations have not been included as abnormal. And yet, as is well known, either of these conditions may be as serious as any form of complicated labour. In extreme cases of either of these conditions—that is, in large breech babies with extended legs, and in backward rotation of the occipito-posterior position—quinization can obviously do no more than fortify the uterus for its unreasonable task.

There are, however, five points about the cases which have undergone this method of treatment which should be effective to some extent even in abnormal cases: (1) Uterine contractions will be strong. (2) Uterine retraction will be good. (3) Following from these two points the puerperal uterus will be empty. (4) Involution will tend to be normal. (5) The patient's resistance to infection will be raised.

Even then we can scarcely expect any great improvement in the course of such difficulties as the large breech or the persistent occipito-posterior presentation; nor can we expect any revolution in such complications as transverse lies, hydramnios, twins, or hydrocephalus. Here again the importance of concentrated ante-natal work must be emphasized.

Placenta praevia, too, occurring as it generally does before the thirty-eighth week, barely enters the discussion. Post-partum haemorrhage, however, certainly requires consideration, and even though it did not occur in this series of cases, no definite conclusion is drawn from the fact. It would, perhaps, be more than human not to wonder if efficient uterine contraction contributed to this fact. It has already been mentioned that no tendency to retained placenta (with its risk of post-partum haemorrhage) has been found with this method. Precisely the same point arises in connexion with the primary and secondary uterine inertia, of which I have no experience in this series of cases. One would almost expect the quinine to have a definite prophylactic effect in patients liable to these conditions. This is an extremely important point for further investigation, because there is no need to emphasize the close connexion between the "inertias" and "prolonged labour," "instrumentation," "haemorrhage," "laceration," and, possibly, severe or even fatal "sepsis."

The view is still held in academic circles that the organisms of puerperal sepsis are mainly introduced from outside, the chief cause of their introduction being "interference." It is not for me to disagree with such a verdict, but I must admit that I consider an empty and contracted uterus as of first importance. This condition

will, I maintain, be fostered by a pre-natal quininization of the patient.

It has been shown previously that subinvolution (or non-involution) is almost an invariable symptom of puerperal fever, and that quinine injections will frequently correct this failure of involution and cure the infection. How much more effective should be a preliminary quininization, which will at least tend to prevent such failure of involution!

There are two other points of great importance bearing upon this subject which have only come to light in this current year. First, it has been shown by Burt-White and Armstrong⁸ that streptococci present in the cervix and vagina at full term (and this is not infrequent) increase rapidly in the uterus up to the third or fifth day after labour, and then diminish. This may possibly be correlated to the other fact, pointed out by Miller and Whitaker,⁹ that the bactericidal power of the blood, after steadily rising during pregnancy, undergoes a rapid fall at or near the time of labour. These two points have prompted me to suggest that the quinine routine should be extended to the end of the first week after labour.

And now, for a moment, let us be thoroughly pessimistic. Let us imagine: (1) poor uterine retraction; (2) blood clot in the uterus (an ideal culture medium); (3) the presence of streptococci—rapidly increasing in the first few days after labour; and (4) a sudden fall in the bactericidal power of the blood. Surely the stage is completely set for puerperal septicaemia! And this after normal labour with no interference!

"Poor uterine retraction" can almost certainly be prevented by quininization, and it is almost equally certain that blood clot will not be present in the uterus. It would be interesting to investigate whether the sudden fall in the bactericidal power of the blood could be delayed or prevented by quinine administration. It does not seem impossible. Now it may be that a mixture of enthusiasm and optimism have led me to exaggerate the possibilities of this method, but personally I do feel most grateful to Dr. Jones for introducing the method to me. In any case the routine is so simple, and so obviously harmless, that any who may be interested can have no possible argument for not trying it out for themselves.

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THE SODIUM SALICYLATE LIVER TEST.

BY

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FOLLOWING the work of Roch and Schiff in 1921, and H. Thiers in 1927 (see *British Medical Journal*, 1928, vol. i, p. 231), it was decided to test the value of the peroral administration of sodium salicylate and its subsequent recovery from the urine in cases of (1) clinically definite liver disease; (2) normal men; (3) clinically suspected liver disease; and to control the results with the levulose tolerance test of Spence and Brett. It is claimed by the authors of the test that sodium salicylate in doses of 0.04 gram can be swallowed by a healthy man and no trace of salicylic acid or sodium salicylate be detected in the urine afterwards, owing to the destruction of the drug by the liver; but in the case of a subject of liver disease quantities of unchanged salicylates would appear in the urine.

The test as described had an attractive simplicity. The subject ingested 0.04 gram of sodium salicylate dissolved

in water at 8 a.m.; all urine passed was then collected until 1 p.m. and tested for the presence of salicylates with acidified ferric chloride (as in the authors' method). Twelve patients were examined, strictly following the authors' instructions. Two had very great enlargement of their livers, due in one case to a severe liver abscess, and in the other case to advanced obstructive jaundice. The remainder were normal men. In no case were salicylates detected in the urine.

It was decided to examine the technique of the authors in detail, with the object of discovering any possible flaws in the method as published. With this end in view solutions of known concentration of sodium salicylate were made in distilled water and in normal and pathological urines, and acidified to varying degrees with a number of different acids, with the result that HCl and H₂SO₄ were found to give the best colour (at an optimum reaction of pH 3 to pH 2 judged by freshly made Congo red and methyl orange paper) on extraction with ether and addition of the reagent. Cooling the treated urine and ether on ice, before use and during separation, materially improved the colour. The optimum strength of the reagent was next the subject of experiment, and it was finally decided to use the following mixture: liquor ferri perchlor. fort. 1 c.cm., concentrated hydrochloric acid 1 c.cm., and distilled water to 500 c.cm. The reaction was made quantitative, a standard depth of colour called "K" being chosen; this was produced by mixing sodium salicylate and the reagent in the relative proportions of 1 gram of the sodium salt to 1,000 c.cm. of the reagent (or 0.001 gram sodium salicylate to 1 c.cm. reagent). It was found that the most accurate results were obtained by keeping the volume of reagent and sodium salicylate as low as possible. A 2 c.cm. quantity of the reagent was used as routine, since it contained enough ferric chloride to produce the full colour from 0.0025 gram sodium salicylate, and experience had shown that it was unlikely that amounts larger than this would be found in 20 c.cm. of the urine. Also 2 c.cm. of the reagent gave a little bulk with which to wash the ether and to retain the extractives after evaporation of the ether. A graph was constructed showing the variation in "K" with dilution; by this curve the quantity of sodium salicylate in any dilution of the reagent could be found in terms of "Ks."

Having thus improved the method of estimation, it was now necessary to discover the optimum amount of ether required for extracting the maximum amount of salicylate that was likely to be found in 20 c.cm. of urine. A number of experiments showed that maximum amounts of salicylate were extracted by 15 c.cm. of ether used in three washings of 5 c.cm.; this quantity of ether was then adopted as the routine. The following procedure was employed.

Treatment of Patient.

The patient fasted from 10 o'clock the previous night. At 6 a.m. the bladder was emptied and the urine collected in marked measuring cylinders. The patient then swallowed 0.04 gram of sodium salicylate in 8 oz. of water. He was given 8 oz. of water to drink every hour from 7 a.m. The urine passed at 6 a.m., 8 a.m., 10 a.m., 12 noon, 2 p.m., and 4 p.m. was collected in separate measuring cylinders, and the volumes noted. The amount of salicylate was then estimated in an aliquot portion of each specimen, using the 6 a.m. specimen to make the standard solution.

The steps in this investigation were as follows. A sample of urine measuring 25 c.cm. was taken, chilled on ice, and filtered through paper; exactly 20 c.cm. was then measured out and rendered acid to Congo red paper (blue colour) with hydrochloric acid. It was then poured into a separating funnel, and extracted with 15 c.cm. of ether in three quantities (keeping on ice). After separating the urine from the ether emulsion the emulsion was broken up with absolute ethyl alcohol and the lower portion was discarded, the ether remaining being measured. Then 2 c.cm. of the reagent was added; the mixture was well shaken and allowed to stand at room temperature until the ether had evaporated. The eventual colour was compared with the standard "K" in a colorimeter, and the result expressed as a decimal of "K." The quantity of sodium salicylate was then calculated from the graph.

The preparation of the standard was as follows. Of the 6 a.m. urine (previously tested, as in estimation for presence of salicylate) 20 c.cm. was cooled and filtered; 0.006 gram sodium salicylate was added, the urine extracted as in estimation, and the final result used as the standard. (Sometimes as many as five standards were made from one urine.)