

while I should prefer to wait for clinical symptoms if he is older. An essential thing in these cases is that the patient's private doctor is informed.

The generally accepted opinion that a positive W.R. means that the syphilitic infection is still active is based, so far as I can see, mainly upon the following two observations: (1) that the W.R. generally becomes negative during the treatment that cures the manifest syphilitic symptoms; (2) that a formerly negative W.R. can be changed into a positive one, when the old disease breaks out again or new symptoms occur.

From the first observation no other conclusion may be drawn at the moment than that the positive W.R. is influenced by the treatment; it does not justify the assumption that because the W.R. has become negative the patient's syphilitic infection has been cured. The second observation will have no value in this connexion until it has been proved that the change from a negative into a positive reaction is almost always followed by clinical symptoms, or that these arise much more frequently in the presence of a positive than of a negative W.R. We are, so far as I know, still waiting for the answer to these questions—an answer which only can be given by examinations made on a great number of syphilitic patients through several years, watching for new syphilitic symptoms or changes in those already existing and comparing them with the results of the Wassermann test.

When among 114 cases of syphilis we are able to discover no less than 30 in whom the syphilitic infection can only be discovered by the examination of the blood, in spite of the fact that the infection in many of the cases dates from several years back, this striking observation throws a different light on the prognostic value of the positive W.R. than that mentioned above, and the question arises, Where in the body are the substances formed which produce the positive W.R.? To the five post-mortem examinations mentioned above I am able to add two more. One of the patients (No. 7 in Table III.) died later; a careful examination of all organs, including the brain, could detect no syphilitic changes whatever. In the case of another patient, a woman, 72 years of age, who had been a prostitute for several years and had contracted syphilis when 20 years old, I could detect only an Argyll Robertson pupil as a clinical sign of syphilis; cerebro-spinal fluid was normal in all respects; the blood showed a positive W.R. (0-60-100) on three separate occasions. She died from carcinoma of the stomach; at the post-mortem examination I could not find any sign of a syphilitic change in the brain or any other organ. A careful microscopical examination of brain, liver, aorta, kidneys, adrenals, pancreas, and spleen showed only senile changes and a slight chronic nephritis due to arterio-sclerosis.

It is difficult to bring these findings into accordance with the generally accepted opinion that the positive W.R. indicates a still active syphilis, and that the antibodies that produce the W.R. are formed in the organs where the syphilitic inflammation has taken root. Does the positive W.R. in these cases indicate that somewhere in the body, perhaps in the bone marrow, there still is a depôt of spirochaetes from where the antibodies come, or does the positive W.R. mean that the syphilitic infection is dead, while the antibodies are still present in the blood? If the first supposition is right we find an analogy in the Widal reaction, which sometimes persists for years in patients treated for typhoid fever; if the second comes nearer to the truth, the analogy lies in the Pirquet reaction in tuberculosis, which is still present even if the specific lesions are calcified.

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THE ACTION OF QUININE ON PREGNANT UTERUS.

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THE physician in the tropics is frequently called upon to treat an attack of malarial fever in a pregnant patient, and is invariably asked his opinion on the effect that quinine will have in precipitating labour. Our knowledge on the action of this alkaloid on pregnant uterus has, up till now, been based mainly on clinical experiences. We know that quinine can induce labour, yet if given as an ecboic agent it often as not completely fails. H. P. Dimmock (1893) considered, as the result of a large practical experience gained at Bombay, that quinine in the ordinary therapeutic doses of 5 to 10 gr., three times a day, could be given with safety during pregnancy. W. C. Swayne and E. Russell (1919) discussed in 1919 the trial of a herbalist who was tried before the Recorder at Bristol on a charge of procuring an abortion by quinine. The Recorder, in his summary, asked the jury to decide whether quinine was a noxious drug: (1) in ordinary doses, (2) in large doses. The jury replied to (1) No; to (2) Yes, and these answers express the popular and current opinion held on the ecboic action of quinine. J. E. Atkinson (1890) in an able summary of the clinical evidence considered that the ecboic action of quinine was largely due to an idiosyncrasy of the patient. His conclusions were as follows:—

- (1) The cinchona alkaloids have not a fixed and definite influence in causing contractions of the uterus.
- (2) An oxytocic action is occasionally produced by these remedies. Their action depends on idiosyncrasy, as in the other idiosyncratic reactions to cinchona, it is impossible to tell in any given subject its manifestations.
- (3) There is some evidence that the action is only excited under large doses, and in debilitated subjects.
- (4) Cinchona and its derivatives should be employed during pregnancy with great circumspection, and should be at once withheld upon the supervention of symptoms indicating a uterine motor influence.

The majority of the writers on this subject have failed to consider a very important additional factor that occurs during the course of a malarial attack—viz., death of the foetus from the effects of high temperature. The action of quinine in controlling the malarial fever, and so preventing inter-uterine death of the foetus, far outweighs any effect this drug may have in precipitating labour. The ecboic effect, as I will now proceed to show, only occurs under certain conditions.

Technique.

The test animal was killed, and the uterus was excised as rapidly as possible and placed in a bath of Ringer's solution containing traces of magnesium chloride at 37° C. After opening the abdomen an incision was made through the centre of the vagina, the cut vaginal end was lifted up with forceps, and the broad ligament divided throughout its length so as to free the left horn of the uterus and ovary on this side. The right horn of the uterus was divided from the left by cutting through the upper end of the cervix. The left horn and its foetal contents (moderately advanced in gestation) were removed to the bath. The vaginal end was fixed to a glass tube bearing a platinum needle, and the ovarian end by a platinum needle which was attached by a hair to a writing lever. The recording of the contractions was done on the drum by a glass frontal writer, described by Lovatt Evans (1919). The bath was kept at a constant temperature of 37° C., and a continuous supply of oxygen was maintained by means of a fine spray of this gas delivered from the bottom of the glass holder fixing the vaginal end. Except in one experiment the lever at the writing end was counterbalanced by a heavy weight. The bath, apparatus, &c., was of a general type described by H. H. Dale and Laidlaw.

The standard base solution was prepared as follows:—

One g. of anhydrous base was dissolved in 27 c.cm. N/HCl to form the soluble bihydrochloride, and about 120 c.cm. of distilled water were added to make the volume up to 150 c.cm.; 27 c.cm. of N/NaOH were slowly added, constantly

shaking in order exactly to neutralise the whole of the hydrochloric acid. The volume was then made up with distilled water to exactly 200 c.cm. in a measuring flask. The standard solution was a 1-2000 solution of anhydrous base in normal saline—i.e., 1 c.cm. contained 0.5 mg. of anhydrous base. The requisite amount of NaCl was formed by the action of the HCl and NaOH. This solution was warmed over a water-bath and added to the uterine bath in the required doses. Quinine and the other cinchona alkaloids can only circulate in the blood in the form of a base, which acts as an alkali; for this reason the base was chosen instead of acid salts.

The Effect of Quinine Base on the Pregnant Uterus.

In a paper read before the Therapeutic Section of the Royal Society of Medicine I pointed out that the dextrorotatory cinchona alkaloids—i.e., cinchonine and quinidine—had a greater action than the laevorotatory isomerides—i.e., cinchonidine and quinine—in increasing the amplitude and rhythm of uterine contractions in non-pregnant guinea-pigs. This finding probably holds good for pregnant muscle as well, but I should have required much more material conclusively to prove the point, as the variations in response to different stimuli are considerable when one is testing pregnant uterus. As the object in this research was to explain the action of quinine on the pregnant uterus, my tests were mainly carried out with this alkaloid. One can safely say with regard to the action of these cinchona alkaloids, that whatever effect quinine has on pregnant uterus, the others will only differ from each other in degree of action.

TEST 1.—*Guinea-pig's uterus.*—4 mg. of quinine base was allowed five minutes' contact and was then thoroughly washed away with three changes of Ringer's solution at 37°C. The capacity of the bath was 175 c.cm., this corresponds roughly to a concentration of 1-44,000. After the uterus has settled down to its normal rhythmic contractions 4 mg. of quinidine base was next allowed five minutes' contact. After washing the uterus free from quinidine cinchonine was tested, but owing to the insolubility of the base the same dose of alkaloid was tested, dissolved as a hydrochloride. All three alkaloids caused a marked increase of tonus in concentrations of 1-44,000. As a result the uterus is contracted rigidly round the foetus. The membranes remained intact in spite of the contractions, as the rigidly contracted os gave sufficient support to prevent their rupture.

TEST 2.—*Rat's uterus.*—Guggenheim (1912) showed that histamine, which caused a marked contraction of the uterine muscle in all other species of animals, when tested on rat's uterus caused relaxation instead of contraction. In this test the pregnant uterus of a white rat was used, and the four alkaloids quinine, hydroquinine, quinidine, and hydroquinidine were tested alternately. The alkaloids were made up as a 1 per cent. solution of anhydrous base dissolved in the requisite amount of N/HCl to form bihydrochlorides. 2 mg. of each alkaloid were placed in a 150 c.cm. bath for five minutes, and then thoroughly washed away with Ringer's solution. The uterus was allowed to settle down to the rhythmic contraction of the excised pregnant uterus. This test shows that quinidine and hydroquinidine are slightly stronger in their action on rat's uterus than quinine and hydroquinine. With none of the four alkaloids is the amplitude of the normal rhythm increased; the rhythm is accelerated and the relaxation diminished, so that the main effect is some increase of tonus. There was no dilatation of the os uteri.

Effects of Different Concentrations of Quinine Base on the Pregnant Uterus.

In a recent paper King and the present writer showed that when a single dose of quinine was taken on an empty stomach by one of us, the concentration of quinine in 5 c.cm. of blood varied with the size of the dose ingested, thus:—

(a) After 1 g. of anhydrous quinine base dissolved as bisulphates (approximately 20 gr. of sulphate). The concentrations found in the blood were: at the first hour, 1-150,000; second hour, 1-187,000; third hour, 1-225,000.

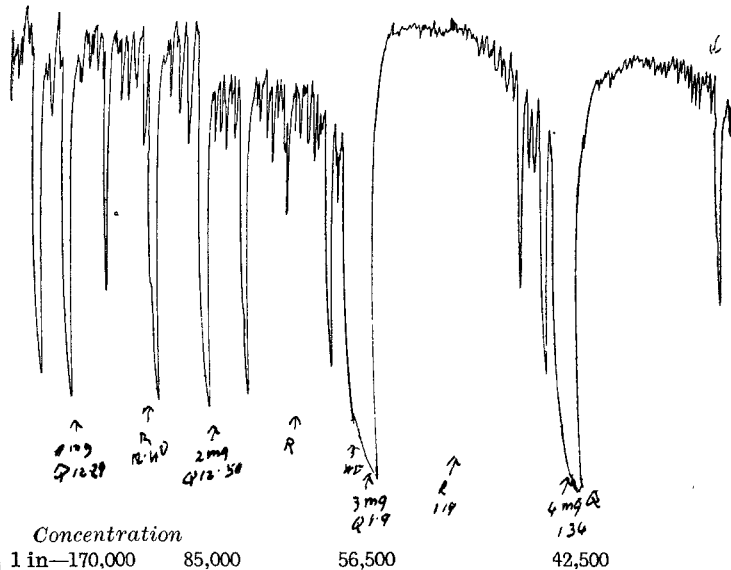
(b) After 0.5 g. of anhydrous quinine base (approximately 10 gr. of sulphate): at the first hour, 1-250,000; second hour, 1-280,000.

(c) After 0.25 g. of anhydrous quinine base (approximately 5 gr. of sulphate): at the first hour, 1-378,000; second hour, 1-750,000.

These results indicated the necessity of testing the effect of different concentrations of quinine on the pregnant uterus.

TEST 3.—*Guinea-pig's uterus.*—In this test increasing doses of anhydrous quinine base commencing with 0.5 mg. were added at intervals of two minutes without washing out; the amount was gradually increased until a total of 4 mg. had accumulated in the 150 c.cm. bath. This concentration of 1-37,500 produced a state of persistent tonus previously described, and to show its sustained character it was recorded for 30 minutes. This test shows that with a 0.5 mg. dose—i.e., 1-300,000 concentration, there was no effect seen. With 1 mg.—i.e., at 1-150,000, the amplitude was increased and somewhat sustained. It was not until a concentration of 1-37,500 was attained that the uterus was maintained for a space of 30 minutes in a state of high tonus.

TEST 4.—*Guinea-pig's uterus.*—In this test the whole dose—i.e., 1, 2, or 4 mg.—was put into the bath. After each test



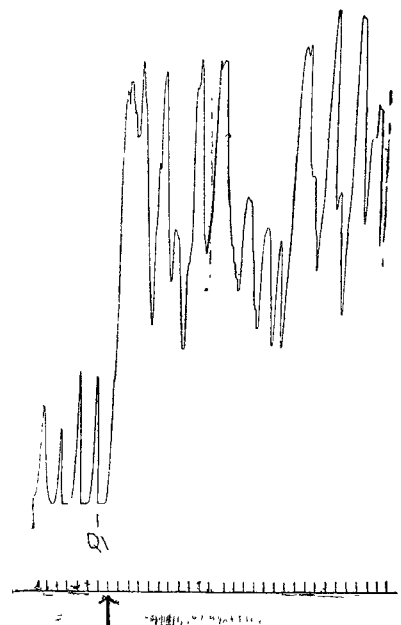
GRAPH 1.—Showing the effect of different concentrations of quinine base on pregnant guinea-pig's uterus. (The mark R indicates the washing out with Ringer's solution.)

the uterus was well washed with Ringer's solution and allowed to relax before the next dose was tested.

1 and 2 mg. of quinine base in a 170 c.cm. bath—i.e., a concentration of 1 in 170,000 and 1 in 85,000 respectively—produced little effect on the contractions of this pregnant uterus. The 3 and 4 mg. doses (1-56,500 and 1-42,500) produced a tonus effect. On this uterus a small hole was now cut over the foetal sac, and a 4 mg. dose was again given. The contraction induced by this dose of quinine forced the membranes through the rent and they ruptured. It was difficult to see what was happening through this depth of Ringer's fluid. After rupture of the membranes one saw that the hole was too small to allow the foetus through. Washing with Ringer's solution caused relaxation of the tonus, which was renewed on adding a further dose of 2 mg., producing a concentration of 1-85,000.

Action of Quinine on the Uterine Muscle.

We know that during labour the longitudinal muscles of the upper uterine segment act as the driving force in expelling the foetus from the uterus; synchronously with this contraction the circular muscles of the lower uterine segment relax to allow the head to pass through this narrow segment of the uterus. In all these experiments with quinine on the pregnant uterus, one saw that the contractions equally affected both the longitudinal and circular fibres. In spite of the violent contractions



GRAPH 2.—Showing the effect of 1 mg. (1-170,000) of quinine base on the pregnant uterus of a guinea-pig which was accidentally wounded. After the quinine was introduced definite labour pains set in and the foetus was driven through the accidental tear in the uterus. (The time record indicates intervals of 10 seconds.)

produced by stimulation of the longitudinal fibres, the os remained tightly closed, so that the foetus still remained in the uterus. On one occasion when a hole was made through the uterine wall the membranes ruptured, but the foetus was still retained.

TEST 5.—The left horn of the uterus, in being cut away from the right horn, was accidentally incised by the point of the scissors. This was not noticed at the time and the uterus was placed in the bath for testing. In this experiment the weight on the lever was small. 1 mg. of quinine was placed in the 170 c.cm. bath, marked Q1 in the graph. A violent contraction of the uterus occurred and labour pains set in, and the whole of the uterine contents were driven through this artificial hole in the side of the uterus. The record is shown in Graph 2.

Summary of the Experiments.

The action of quinine in certain concentrations causes contraction of both the longitudinal and circular fibres of the uterus. The effect produced depends on the concentration of quinine present—weak concentrations 1-300,000 have no effect; concentrations of 1-150,000 produce contractions under certain conditions, whilst a concentration of 1-44,000 produces a tonic spasm, which, if sustained, would cause asphyxia of the foetus from constriction of the placental sinuses. This concentration could only be attained if the patient was nearly poisoned by a large dose of quinine. The degree of concentration in the blood varies with the dose taken and on individual susceptibility depending on the rate of absorption. Cinchonism is correlated with the concentration of quinine present in the blood and varies with different individuals, and is more frequently seen with weak and anæmic persons. Concentrations of 1-150,000, such as occur with large doses, increase the strength of the intermittent uterine contractions, and if some exciting cause was present—e.g., weak membranes or a patulous or dilated os—the pressure produced by the increased contractions might be sufficient to cause rupture of the membranes or dilatation of the os, and so bring on labour.

Therapeutic Recommendations.

1. The controlling of the fever by quinine or other cinchona alkaloids must be the first objective in the treatment of these cases. We know that high temperatures soon cause death of the foetus, and this factor is sufficient to induce premature labour. The mother's temperature should be carefully watched and prevented from exceeding 103° F. by sponging, &c.

2. The avoidance of large doses of these alkaloids. As soon as the diagnosis of malaria is made, which is an urgent matter in pregnancy, quinine or quinidine should be given at once as the case requires. It is better to divide the doses into 2½ or 5 gr. doses given every two or four hours. 20 gr. a day is sufficient, and ample to control any attack of malarial fever.

3. The employment of general methods for the prevention of miscarriage—viz., complete rest in bed and the judicious use of opium in allaying any mental excitement. When the child is dead or the miscarriage inevitable quinine should be given in ordinary doses and the case treated on general obstetrical lines.

I must finally express my gratitude to Dr. H. H. Dale, F.R.S., for permitting me to work in his laboratory, and for the help and advice he gave me during the course of these experiments.

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ROYAL UNITED HOSPITAL, BATH.—At the close of 1920 there was an adverse balance of £18,000 against this hospital. The National Relief Fund has granted the institution £12,500 from the £700,000 set apart to help out the war deficits of voluntary hospitals.

AN UNUSUAL FATAL CASE OF INFECTION WITH B. ENTERITIDIS OF GAERTNER.

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IN a recent issue of THE LANCET, A. B. Rosher and G. Selby Wilson¹ describe a case having many similarities to enteric fever, but due in all probability to infection with the *Bacillus enteritidis* of Gaertner. Their report has recalled an unusual fatal case of infection with the same organism, seen by me during the war, which amplifies many of their findings. The notes of the case are briefly as follows:—

Pte. J., aged 25 years, became ill on Nov. 20th, 1917, with shivering and pains in the head and limbs. High fever was present, without pulmonary or intestinal symptoms, and a provisional diagnosis of trench fever was made. Eight days later the patient suddenly had a "fit," and bit his tongue during the convulsion. Next day he appeared better and was transferred from the field ambulance to a corps rest station. Almost immediately another convulsion took place, and he was sent on to a casualty clearing station, where he was first seen by the writer. After admission, 12 convulsions occurred within a few hours, and he became semi-comatose. A specimen of urine was obtained, but contained only a trace of albumin. On the suspicion that the case might be cerebro-spinal meningitis, lumbar puncture was carried out on Dec. 2nd, but the fluid was quite clear and contained no excess of cells. Signs of pulmonary involvement now developed, and within three days the base of each lung was found to be consolidated. A specimen of urine, examined on the 7th, was decidedly smoky, and contained red blood corpuscles and a large amount of albumin. He died during the afternoon of the 7th, 17 days after the onset of his illness. From Nov. 29th, until death occurred, he remained in a semi-comatose state. Vomiting occurred frequently during the illness, but there was never diarrhoea at any time.

Since the man was in various hospitals no complete temperature chart is available. He is known, however, to have had high fever for over a week after the onset of the illness. On admission to the casualty clearing station the temperature was subnormal, and remained so until three days before death, when it rose to 102° F. at the time when signs of pulmonary involvement became manifest.

Post-mortem.

A post-mortem examination was made 16 hours after death. There was no oedema of the face or limbs. Herpes was present on the lower lip. On removing the calvarium very striking oedema of the cerebral meninges was found. In section the brain substance showed many "puncta cruenta," but no actual hæmorrhages. An excess of fluid was present in each lateral ventricle. The pericardial sac was normal and the heart healthy. The air-passages, from the pharynx down, were removed intact along with the lungs. The trachea was seen to be half-filled with yellowish pus, often in the form of small, worm-like masses. The mucous membrane, when the pus was removed, was found intensely congested and ulcerated in places.

The lungs were voluminous, and showed many petechial hæmorrhages beneath the pleuræ. The upper halves of each organ were somewhat emphysematous, and the finer bronchi in this situation did not contain any pus. The lower parts of each lung were irregularly consolidated, some areas being much firmer than others. In section the appearance was extraordinary. Each small bronchiole stood out as a bright lemon-yellow spot from which, on pressure, a small worm-like purulent cast could be squeezed out. Each of the bronchioles was surrounded by a wide zone of hæmorrhage, forming a ring about the size of a shilling. Further away from the bronchioles the general appearance of the lung tissue was an almost uniform deep purple colour. The results of examination of the pus from the bronchi will be referred to later on.

The peritoneum was normal, and on careful examination of the stomach and intestines no trace of ulceration or of any inflammatory change was found anywhere. The faecal material in the colon was of normal type, and contained neither mucus nor blood. The liver was somewhat fatty, but not otherwise unhealthy. The spleen was distinctly enlarged, and the pulp very soft. The kidneys presented

¹ A. B. Rosher and G. Selby Wilson: A Case of Enteric Fever due to the *B. enteritidis* of Gaertner, THE LANCET, Jan. 1st, 1921, p. 16.