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Thesis for graduation

John⁶⁷ Liddell M.B. Ch. (1882)

The action of Iridine considered in connection
with its effects on the Parturient Uterus



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I

The action of Quinine in connection
with its effect on the Parturient's
Uterus

It is well known that Quinine has the power of exciting contractions in the gravid Uterus. It is mentioned in the ordinary text-books not only as a direct Emmenagogue but also as a ~~abortifacient~~ ^{abortifacient}. It is seldom used in this country as an Oxytocic though it is occasionally used as such in America.

In 1885 I began to make observations of the action of Quinine with the object of ascertaining whether or not reliance can be placed upon it as an oxytocic. The observations have been principally during prolongation of the second stage of Parturition.

In looking for a remedy to alleviate or remove a pathological condition it is necessary to understand the normal structure and function of the affected part and to ascertain the cause of

of the abnormal conditions. Therefore before giving the results of these observations it will be as well to consider (1) The nature of Uterine Contractions (2) The state of the circulation in labour (3) The causes of the prolongation of the second stage of Parturition -

I The nature of Uterine Contractions

The muscular fibre of the Uterus is striated, and the Uterus is mainly composed of this tissue which is under the control of the nervous system. The nerves are principally derived from the Sympathetic system, partly from the Cerebro spinal through the sacral nerves -

Involuntary muscle has a greater tendency than voluntary to rhythmic contractions. It has been shown that the conditions for rhythm are contained in contractile tissue itself. Probably however a stimulus which may be slight is required to induce the rhythm in involuntary muscle - Mechanical distension is a powerful stimulus in exciting contractions, a circumstance to be borne in mind in connection with Parturition - The veins of a

1. Normans - Phil Trans Vol 96 part 1: Vol 97 part 2

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bats wing were observed by Luckesinpi
& Pulsato after the death of the
animal when artificial circulation
was maintained. Engelmann² observed
that in the Uterus in which no nerves
have been found rhythmical contractions
occurred when the Uterus was exposed
showing that it may contract without
extra stimulus; and when the animal
was exhausted and the excitability
of the Uterus was thus diminished
that distension increased its rhythm.

The contractions of the parturient
uterus are rhythmic in character. They
begin feebly, then a tolerably rapid
accession of strength until a maximum
is reached, there is a continuance
of this maximum and this is followed
by a gradual decadence until the
'pain' ceases. There is a varying interval
between one contraction and the next
i.e. there is a state of diastole or
repose. This interval is of immense
importance. Unless it occurred,
on the one hand, the mother's powers
would be exhausted, and on the
other, the placental circulation would
be interfered with so as to cause the
death of the child.

1 Pflüger's Archiv Bd 26 p 465 } Justici by Lancer Smith
2 " " " Bd 11 p 267 } Pharmacology & Therapeutics

There is an analogy between the parturient organ and a slowly beating heart. They are both independent of volition; their contractions are rhythmic; and may be inhibited or excited. During labour inhibition may occur - the entrance of a stranger into the lying-in room may cause an entire cessation of pains. On the other hand sudden emotions may excite labour. Prof. Dr. Foster's Supports remarks that the rhythmic character of the contractions suggests that the cause is seated as it is in the heart, in the organ itself. This view is supported by the fact that after destruction of the spinal cord if the uterus be stimulated contractions occur similar to those of parturition. On the other hand experimental investigations show that the contractions mainly depend on the spinal cord and these experiments are supported by general evidence. Kobrij² has shown that there is a uterine centre in the lumbar region. This may be directly and also reflexly stimulated - Von Basch & Hofmann³ in their experiments found in the dog two paths along which afferent impulses pass from the central

1 Textbook of Physiology p 628
 2 Kobrij - Verchow's Archiv Bd 76 1879 page 1
 3 Basch & Hofmann Wien. med. Jahrb 1874 p 4 } quoted by Dr. Foster

V

nervous system, one a sympathetic tract the other a spinal. They assert that the former contains vaso-constrictor the latter vasodilator nerves. Rohrig found two efferent paths in the rabbit. He also found that reflex movements were more easily induced by central stimulation of the Sciatic and Crural nerves than of the brachial or other nerves of the anterior part of the body, and that very energetic movements take place when the central ends of the Brachial nerves are stimulated. This is an important observation in connection with Parturition. According to Kerner there is another centre and that is seated in the Brain - Stimulation of the Cerebellum, Crus Cerebri, Corpora Striata and Optic Thalami excite uterine contractions - Whatever may be the cause of the origin of labour whether it be automatic or reflex, clinical evidence supports the view that the continuance of the contractions is largely dependent on reflex action. In normal labour so soon as the membranes are ruptured and the presenting part of the Child comes in contact with the Parturient Passages Labour progresses

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more rapidly. As more and more of the fetus comes in contact with the vaginal walls the stronger and more frequent the pains become. It is then too that the abdominal muscles come into play. The reflex action is further evidenced by the fact that introduction of the finger through the Os and sweeping it round or stretching the Os, or stretching the perineum especially when the presenting part is low will cause an increase in the force and frequency of the contractions.

The state of the Circulation in Pregnancy and Parturition

Not only is there an increased quantity of blood directed to the uterus in pregnancy and parturition but the blood pressure of the general circulation is increased. Ballantyne states that there is a further increase of tension in parturition reaching a maximum during a uterine contraction. He gives no explanation of this but ^{undoubtedly} ~~probably~~ the increase in pressure is due to the large quantity of blood suddenly drawn from the uterus into the general circulation.

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Prolonged labour depending on defective action of the expulsive powers.

Lingering or prolonged labour may be due to many causes. Some are due to mechanical obstruction e.g. rigidity of the passages others depend on deficient or irregular action of the expulsive powers.

The expulsive powers are the Uterus and the abdominal muscles. From

the foregoing considerations it is evident that prolongation due to defective action of the Uterus may depend on a variety of causes (1) There may be an im-

perfect development of muscular tissue

(2) There may be exhaustion of muscular tissue (3) The nerve supply may be in

fault (4) The circulation through the Uterine vessels may be imperfect.

In connection with the second cause it has been shown that fatigue renders the contractile wave of muscle slower, longer, and smaller. Exhaustion of an animal has the same effect. When a muscle contracts a chemical change of the nature of oxidation takes place in the muscle, and certain waste products occur e.g. Carbonic Dioxide and lactic acids. Fatigue is probably due to the accumulation in the muscle

of waste products. Free circulation of blood through the muscle tends to remove these. Kroecker has shown that opidising substances such as Potassium permanganate of Potash added to a salt solution (NaCl) and circulated through the vessels of a muscle quickly restore it. These two last points are to be borne in mind in connection with Quinine

Treatment of Prolonged Labour

There are three modes of treatment of cases of prolonged labour depending upon failure of the expulsive powers. These are (1) The administration of oxytocic remedies (2) Pressure of the Uterus through the abdominal walls (3) Instrumental interference. Of these I shall consider Oxytocic Remedies

Oxytocic Remedies - Several are mentioned in the books but the only one upon which reliance has been placed is Ergot. I shall therefore consider its action & then that of Quinine.

(1) Ergot -

According to Handley Bunting the active principles of Ergot are still imperfectly known
 1. Kroecker - Ludwig's Arbeiten 1871. p. 183

Known - Robert's researches are the most recent and he states that it contains three active principles viz Sympotinic Acid, Sphaerulinic Acid and an Alkaloid Cornutinin. He found that Sympotinic Acid has no effect on the Uterus, and that it lowers the blood pressure. Sphaerulinic Acid produces tetanus of the Uterus and an increase of blood pressure. Cornutinin produces Clonic movements of the Uterus and causes contractions of the blood vessels. (See Tx² remarks these were inadvertently omitted)

→ Sympotinic Causes contraction of unstriated muscle throughout the body - Probably its action is on the uterine muscle. Kohrj however states that after destruction of the lumbar centre Sympotinic has no effect on the Uterus. If that be so then its action must be on the Spinal centre.

(B) The action of Quinine

The action of Quinine on the Parturient Uterus is unlike that of Sympotinic. Quinine strengthens and prolongs the contraction, and it increases the frequency. It maintains the rhythmic character of the contractions. I have used the Sulphate in 151 Cases during prolongation of the second stage

1, Kohrj - Practitioner 33. p 409

These active Principles are not in general use and either Bouyer's Ergotin or Extract of Ergot is used - The action of them is to produce tetanic contraction of the Uterus with occasional increases of violence but they do not increase the strength of the contractions. There is no complete relaxation of the uterine muscle as in ordinary labour. This condition of persistent contraction in protracted labour results in irritation of the system and is the chief cause of the dangerous symptoms in this condition. Thus unless speedy delivery occurs there is great danger to mother and child. Ergot ought never to be given unless the presenting part rests on the Perineum and there is no mechanical obstacle to immediate delivery or unless one is prepared to effect delivery by forceps so soon as its action commences

see IX'

1 Playfair - The Science & Practice of Midwifery
Vol II p 9

It is generally stated that Small doses increase the strength of the circulation but that large doses diminish the blood tension chiefly by weakening the heart, partly by paralyzing the vasomotor centre and thus causing dilatation of the arterioles. Wild's² experiments led him to conclude that it acted on the vessels themselves

1 Hurley - Phil Trans - 1865 p 678
2 Wild - British Medical Journal 1884. Sep 3. p 500

X

in from 2 to 5 grain doses, generally repeated twice, in half hour intervals. The effect was usually evident in from twenty to thirty minutes. In no case was it followed by a continuous or tetanic contraction, the rhythmical character was always maintained. In some cases however no action followed the administration. In considering the mode of action of Quinine it will be necessary to examine its effect on the vascular system, on the muscular fibres of the Uterus, and on the nervous system.

The action of Quinine on the Vascular system

Quinine diminishes the process of oxidation in the blood, lessening the amount of Oxygen absorbed and of Carbonic Acid given out.

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1 Hurley - Phil Trans - 1865 p 678

2 Widd - British Medical Journal 1884. Sep 3. p 500

and not on the Vasomotor Centre of the Cord. He found that in the beheaded tortoise there was first contractions of the vessels, then dilatation, and eventually contraction, the quantity of blood then passing being about half of what passed before he administered Quinine.

I have given it to adults principally females in from 2 to 10 grain doses, and with my fingers and with the sphygmograph noted the effect on the pulse. And I now send several series of sphygmographic tracings to show the effect on the pulse. I generally found with these doses that in from twenty minutes to half an hour the volume of the artery decreased, and not only this but that it was more easily compressible. In some cases in from 5 to 15 minutes there was an increase in the volume of the pulse. If the tracings are compared it will be seen that whatever the initial effect may be there is eventually a diminished lumen of the vessel. Frequently there is dilatation with an increased range of movement of the wall and with a well marked pre-diastolic & diastolic wave, and a fall in pressure. The radicals were the arteries
 1 see tracings at end of thesis

observed in all cases.

Professor Rutherford suggests that blood vessels in muscle have an independent or automatic tonicity, that there are vaso-inhibitory fibres in nerves and that when a muscle is stimulated the fibres inhibit the energy of the muscular wall of the arteries and dilatation occurs.

During parturition an abundant supply of blood is required by the uterus. During this phase of physiological activity it develops an enormous amount of mechanical energy derived from chemical energy which is produced by changes in the constituents of the muscle. Oxygen is used up & Carbonic acid given out and in order that this condition of things can go on uninterruptedly a free circulation of blood is necessary.

What the precise action of Quinine is I am unable to say, it may affect the vessels in the same way that it does those of the general circulation, or it may have a special action on them.

I have found that in cases of hæmorrhagic discharge from the uterus as in Endometritis, during the puerperium, during menstruation and in Uterine Cancer, if Quinine was given it was almost

invariably followed by an increased flow. I have found it also produce hemorrhage occasionally during an intermenstrual period. Whatever may be the effect on the uterine vessels during parturition these cases suggest that in other conditions it directs blood to the uterus. I may quote a case in point. On 6th May 1885 I was asked to see a young lady suffering from facial neuralgia. It was exactly midway between two of her periods. I gave her 15 grs of Quinine. In half an hour her neuralgia was quite relieved but at the same time she felt a sharp pain in the hypogastric region and in a few minutes she found hemorrhage issuing from the Vagina.

Action of Quinine on unstriated muscle

Will & others have found that small doses stimulate, larger doses paralyze unstriated muscle. Very large doses cause rigor mortis. Lauder Brunton says that Todd & Nowak have shown that the composition of all the muscles is not the same. He says that muscular poisons do not act alike on all the muscles of an animal, and that the effect will vary according to the chemical composition of the tissue at the time.

Action of Quinine on the Nervous System

Quinine is said by some observers to affect sensory and motor nerves only when applied locally. Willd however states that it has no action on motor nerve trunks but that nerve endings in muscles are paralyzed by it when locally applied. The reflex action of the Spinal cord is diminished especially in the prof-Binz suggest that this probably is due to failure of the circulation.

Quinine produces a pharmacological analgesia. It has little or no effect if the pain be due to inflammation or other structural change. It is in neuralgia that we find its analgesic property exhibited. There is a theory that neuralgia often depends upon hyperemia of the neurilemma where it passes through an opening in bone. The Trigemino has many branches which pass through narrow openings and canals, and it is a nerve frequently affected by neuralgia, especially the supra-orbital. Now this branch is the one upon which Quinine is stated to have the most influence. I would suggest that some at least of the action is due to removing pressure, which is a cause of pain, from the nerve by

diminishing the blood in the Neurolemmas. Relief generally follows in 20 minutes to half an hour after administration, and this coincides with the time that it generally affects the circulation. In support of this view I have found that the cases relieved by Quinine are also immediately relieved by Electricity and the latter constricts blood vessels.

If the action of Quinine were on the Hippocampal region or on sensory nerves it would relieve or abolish pain wherever irritation of a sensory nerve occurred instead of only occasionally as in Neuralgia. Probably its action on the Spleen, in diminishing enlargements of that organ, is due to its ~~to the~~ effect on the circulation.

Notes of cases of Labour where there was
prolongation in which Quinine was ad-
ministered -

I have taken ^{pulse} tracings during the 'pains' in lingering cases before and after administration of Quinine but owing to the movements of the patient they cannot be relied upon.

To save needless repetition I may say that in the following cases there was no

mechanical obstruction to cause delay.
These selected cases may be considered
representative.

I N^o W. April 43 - Thirteenth pregnancy
Nov 6th 1885. States that at 3. am on the
2nd inst she felt a sharp pain in the
abdomen followed by a sudden rush of the
Liquor Amnii - She has remained in bed
since then but has had no pains. On
Examination I found the Os nearly fully
dilated & the head resting on the Perineum.
At 3 p m, 5 grains of Quinine were given
at 3. 20. Pains commenced - At 3. 30
another 5 grains were given and within
a few minutes labour was fully established.
The contractions were frequent and strong.
At 4. 55 she was delivered of a healthy
female child - The passages were
soft: cavity roomy. Made an excellent
recovery.

II N^o F. April 30 Primipara
April 15. 1886 - Pains commenced at 2
a.m. At 11.30 a.m. they occurred about every
20 or 25 minutes - Passages moist parts
rather resistant. Pains continued all day.
April 16th - Os thinned out about size of
half-a-crown at 11.30 am. Pains have

very little effect on the head. Ordered 5 grains of Quinine to be given every two hours. About 1/2 hour after each dose the pains were more frequent & stronger, but this effect lasted only for an hour or a little longer. at 8.30 pm head in cavity of pelvis and as patient was exhausted I delivered with forceps. The walls of the uterus felt thin and after delivery the contracted organ was much smaller than usual.

III Mrs S. aged 30 - Third pregnancy
 July 25th 1886. Os dilated at 10.45^{am}. Head resting on brim not engaged. Contractions painful but not expulsive - gave 5 grains of Quinine - At 11.10 pains became stronger and soon after more frequent - at 11.15 another 5 grains were given - Pains then became very strong & expulsive. At 11.55 delivered of a girl weighing 8 lbs. She stated that at her previous confinements Syph was given & that it caused her great pain, There was a continuous pressure & she never had a chance of getting her breath. She had fewer & less severe afterpains than in her two previous labours.

IV - Mrs D Apr 28. Third labour

Aug 14th 86 - Saw her at 8.30 p.m. Stated that membranes ruptured last night about midnight. Head in pelvic cavity in the right ~~Acipito-~~ sacro-iliac position - Passages moist - Pains few and feeble.

Aug 15th At 9. am. Said to have had few pains in the night only acute twitches gave her 5 grs of Quinine Sulph. At 9.25 pains returned at 9.45 they were most powerful and spontaneous occurred every few minutes at 10.45 child born - Very few after pains and only slight

V Mrs C Apr 27 - Second labour

March 26 - 1887. at 1 pm pains severe sharp lasting about 1 minute occurring every 10 minutes Os thin about size of half a crown - Labour commenced at 1. a.m. At 4.45 Pains severe, but have no propulsive effect Os dilated. Patient very tired. At 4.50 gave her 5 grains of Quinine Sulph. at 5.20 Pains stronger have more effect on the head, gave her other 5 grs. Pains increased very much in power occurred every 4 or 5 minutes - At 6.10 she was delivered of a fine female child - Had very few after pains

VI Mrs J aged 28: 3rd Labour: strong & healthy
 Sep 21. 1888 - Labour began at 3 a.m. At
 9.30 found Os thinned out $\frac{2}{3}$ was dilated. Pains
 frequent and strong. At 9 p.m. Os
 fully dilated, Pains fable. Membranes were
 ruptured & immediately Pains become stronger
 At 10 p.m. Pains again fable & infrequent - gave
 her 5 grs of Quin. Sulph. at 10.30 other 5
 grs. within a few minutes the Pains became
 much stronger and more frequent - At 11.40
 the child was born.

VII Mrs W. aged 37 - 6th Labour - Short
 Oct 28. 1889 - Pains commenced at 10 p.m.
 the membranes having ruptured at 6 p.m.
 Oct 29. Os dilated, head engaged. Pains
 frequent but have little power - Patient
 complained of feeling weary and exhausted.
 At 11 a.m. gave her 10 grs of Quinine At
 11.20 Pains began to be stronger and more
 profuse. At 12.30 delivered of a fine
 healthy boy. After expelling the Placenta
 found the Uterus contracted into small
 bulk.

VIII - Mrs D. 34. Debeate weakly small woman
 4th Labour. Quinine had no effect in this
 case
 Sep 11th 1888 - Labour commenced at 1 a.m.

Pain strong at first - 10.30 a.m. mem-
branes ruptured & well dilated. Pain
continued very faint. At 3.5 p.m. 5
gr of Quinine Sulph from pain seemed slightly
stronger about 3.35. Other 5gr given at 4.30.
Pain then became less strong and the
patient was very exhausted. I therefore
delivered her with forceps. Child weighed
10 lbs 2oz. 22 inches in length, female.
Sep w. Mother & child are both very well

In conclusion Quinine may be
considered an Oxytocic remedy. In cases
of delay pressure of the uterus through the
Abdominal Parietis is very valuable.
Kneading or Massage when it can be applied
has a very marked effect. It restores
the muscular power by removing the
waste products, the action is similar to
a complete circulation of blood through
the uterine vessels. This valuable method
does not seem to be generally recognized.
In some cases neither it or Pressure can
be applied on account of great tenderness
of the uterus. Instrumental interference
may be considered a 'dernier resort,' and
is frequently objected to by patients and

1 Zabudowski - Central. f. d. Med. Wien 1883
No. 14. p. 241. Quoted by Brunton

their friends. In these cases when Pressure
or Kneading cannot be applied, or
Instrumental interference is objected to
Quinine may be tried.

I have tried this drug in 151 cases

It failed entirely in	8
The contractions were stronger & more frequent in	91
The contractions were decidedly stronger and more frequent in	52
	151

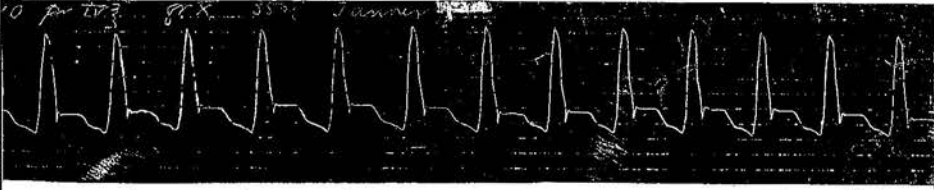
In the cases in which it entirely failed
the volume of the pulse was less & it was
more easily compressible, even before giving
Quinine. The cases in which it gave the
best results the pulse was only slightly
affected. Quinine affected the pulse
in all cases, in the manner stated.
In some cases lately I have given Brandy
along with Quinine and in most of these
cases the contractions were stronger and
more frequent, but I cannot adduce
sufficient evidence on this point.

The valuable discoveries of Professors
Fraser and Cram-Brown & of Schroff
who showed that by the modification
of the chemical constitution of a
drug it is possible to modify the
physiological action lead me to hope

that a modification of the chemical constitution of Quinine ($C_{24}H_{24}N_2O_2 \cdot 3H_2O$) may produce a drug which like Quinine stimulates the uterus to rhythmical contractions, but unlike it possesses a stimulating effect upon the heart. The introduction of such a drug would be of immense service in a large class of cases

John Liddell M.B. Cant. 1882
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 Hants

Tracings taken during the second stage of labour
between two pains. The tracing before 5 grains
of Quinine was from has been mislaid



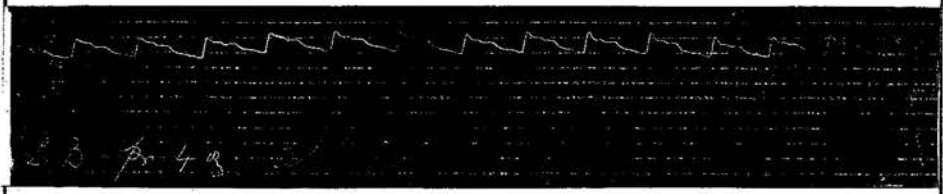
taken from left radial - 35 minutes after
10grs of Quinine



taken from left radial 1 hour after ad-
ministration of Quinine. It shows that
the volume of pulse was less, also ^{blood} pressure
lowered, i.e. less than at 35 minutes after

L. B. April 20. Left Radial

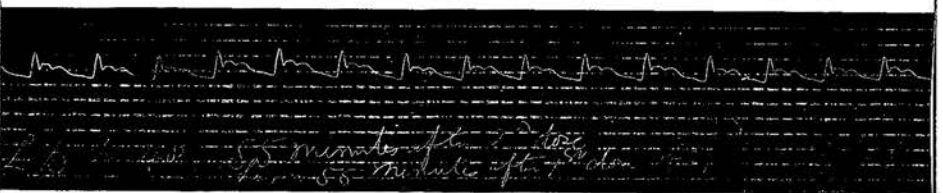
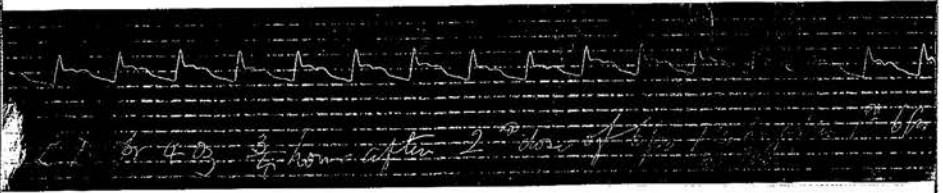
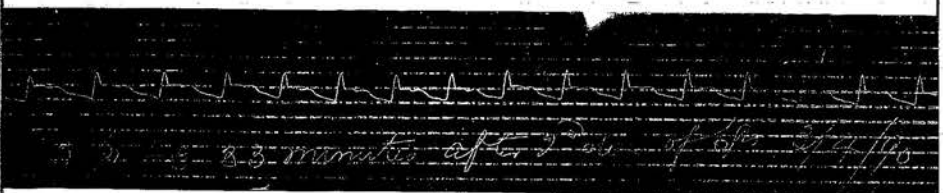
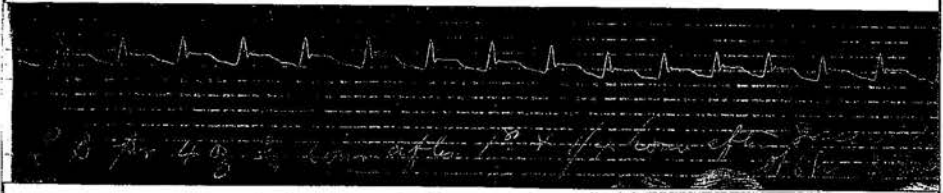
Before



1/2 hour after 6 ps



1/4 hour after and dose of 6 ps

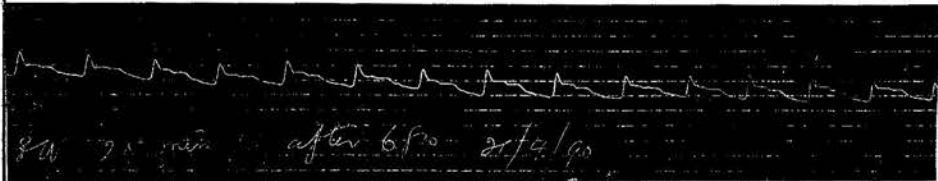


G. W. apt 21 - Left Radial

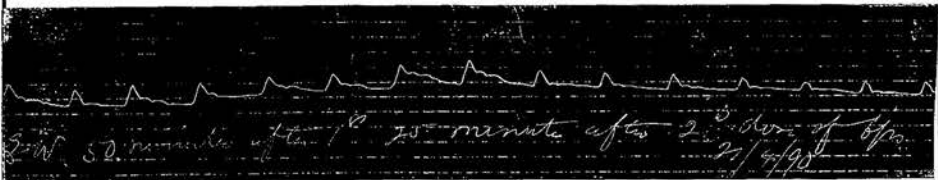
before



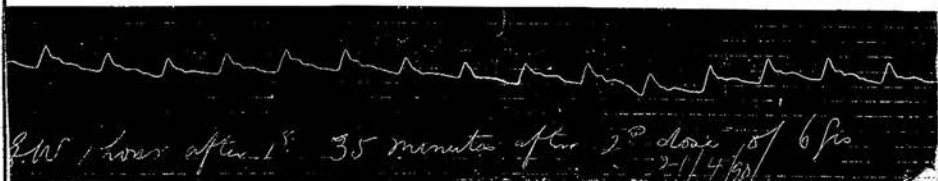
after 6 grains



after 2nd dose
of 6 grains



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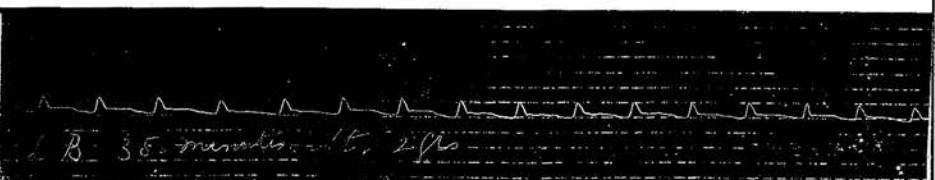
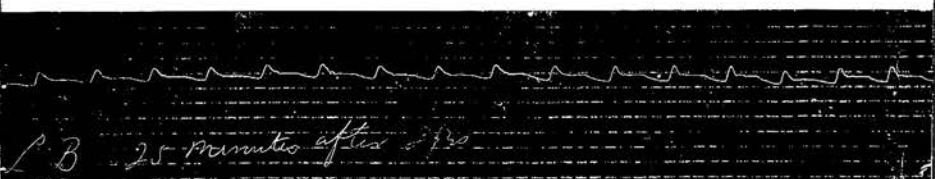
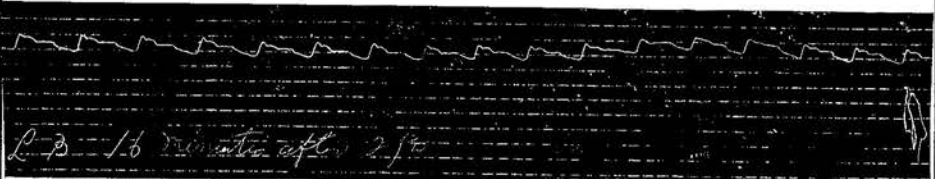


L. B. April 20 Left Radial

before

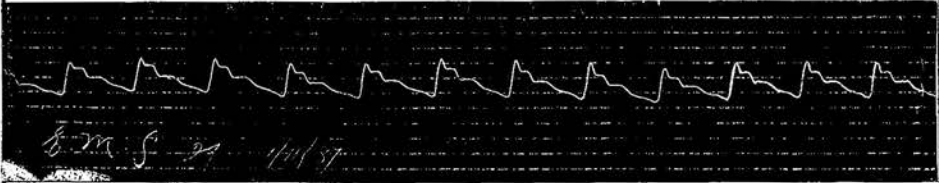


After 2 grains

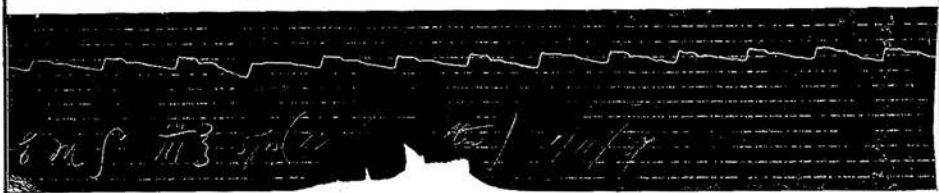


S. M. J. aged 55 Left Radial
mitral murmur

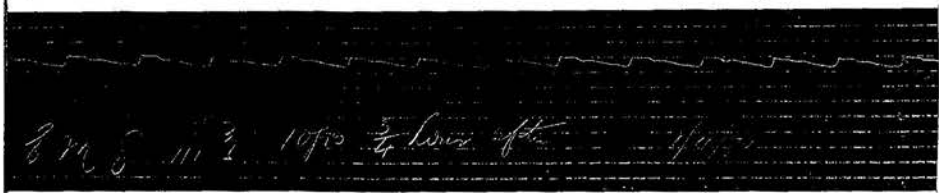
before



after

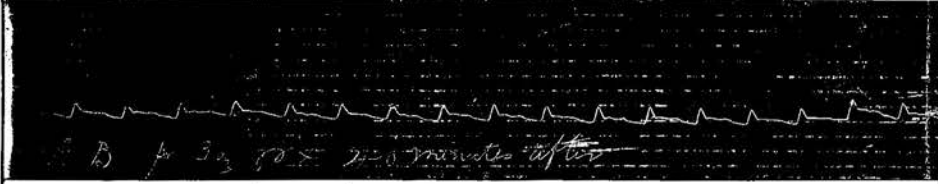
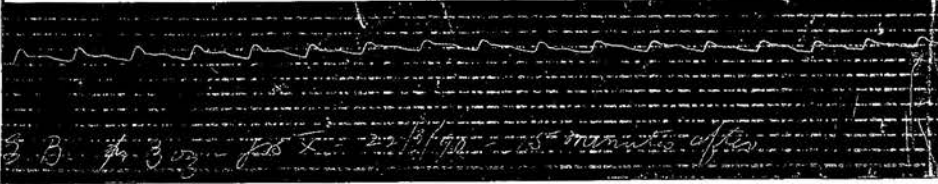
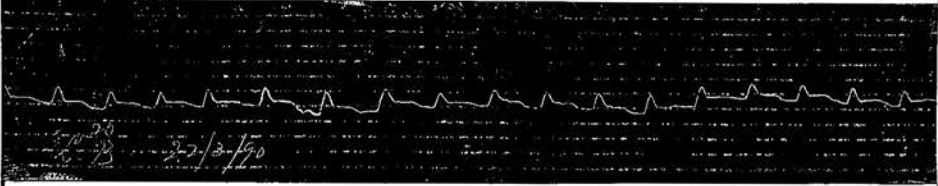


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L. B. Lpt Rudel

Before



After 10/10

4

4

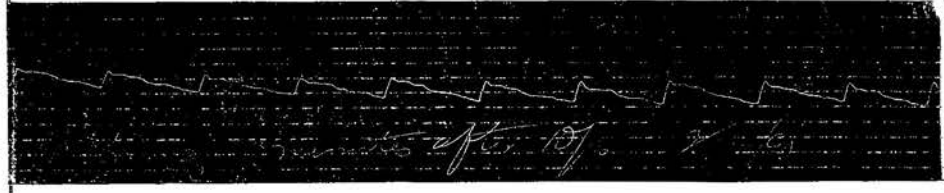
S. W. and 30

left radial

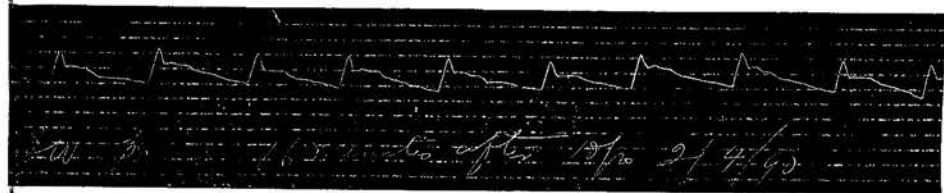
before



after 10 p.p.m.



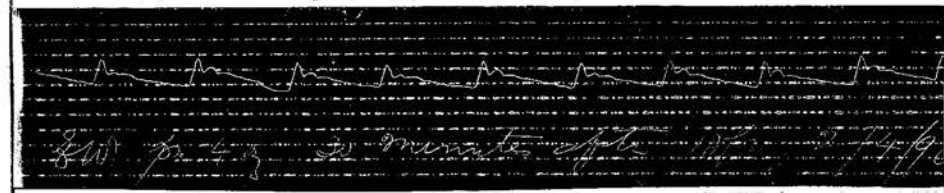
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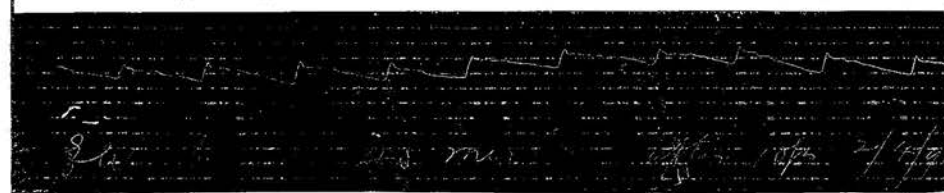
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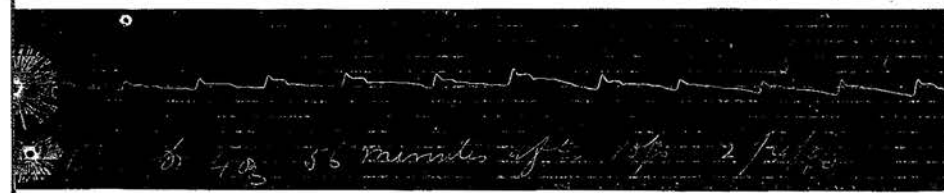
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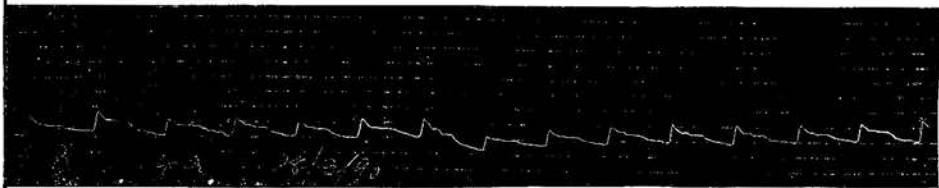


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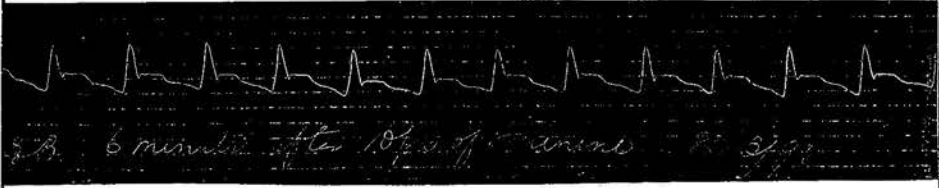


L. B. aged 30.

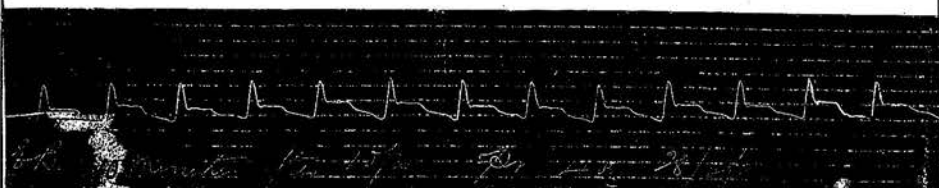
Before



after 10/20



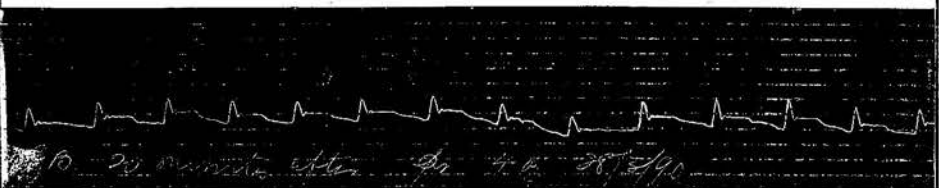
11



12



13



14



15



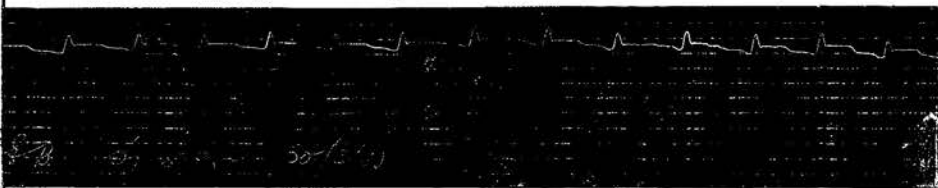
16



L. B. 20

Left radial

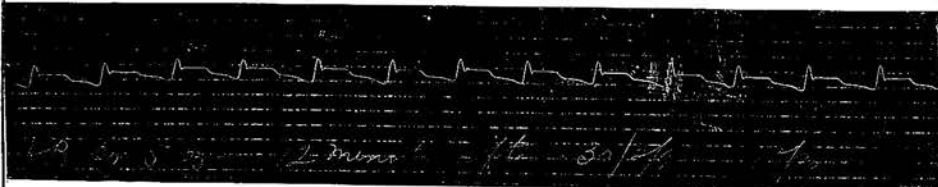
Before



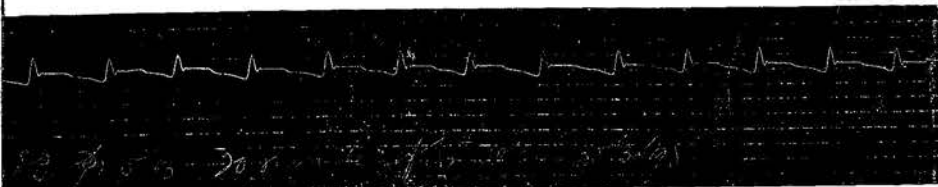
after 10/20



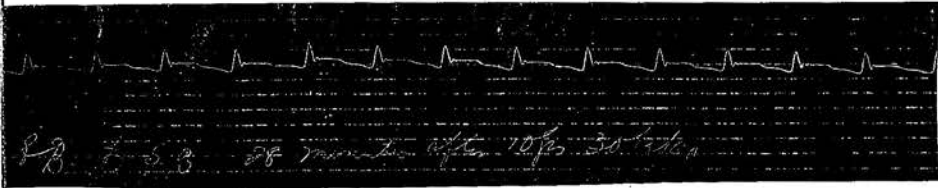
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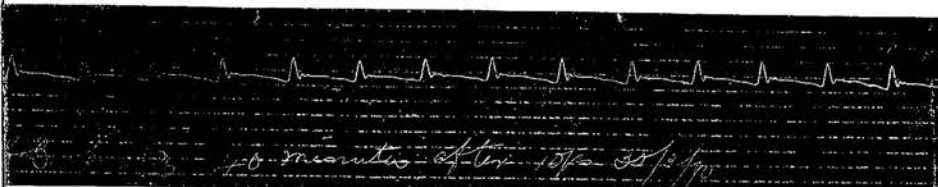
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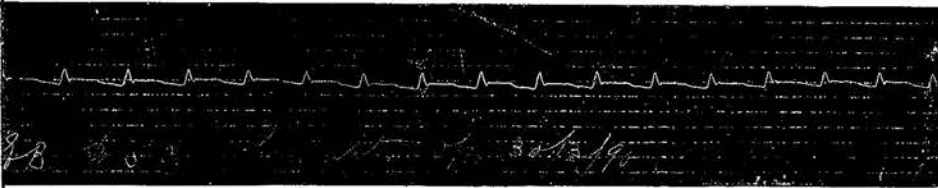
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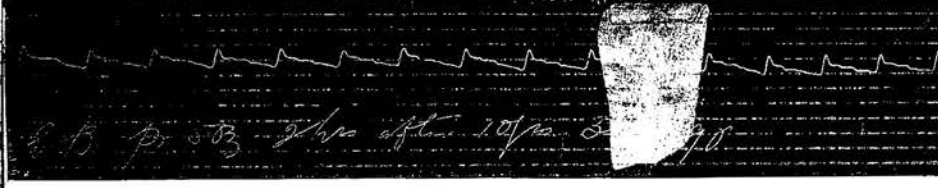
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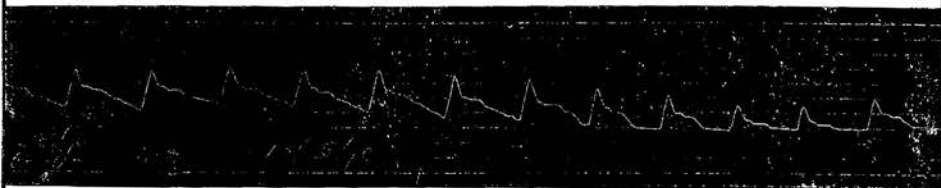


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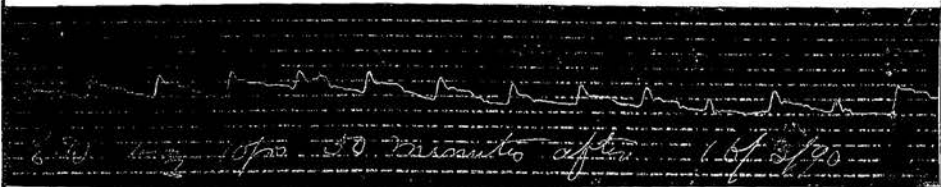


Taken from left Radial
S.W. April 21

before



after



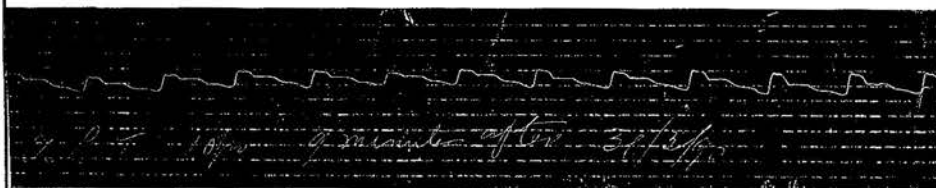
Taken from Left Radial -
a.l.T. 30

before



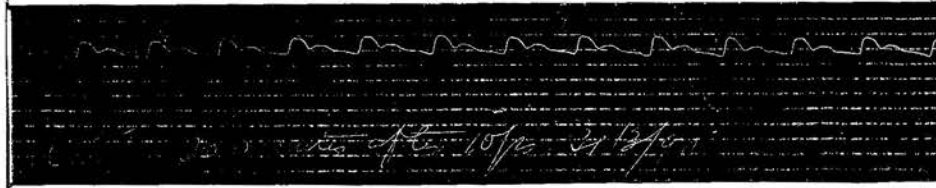
before 10 ppm of Quinine

after

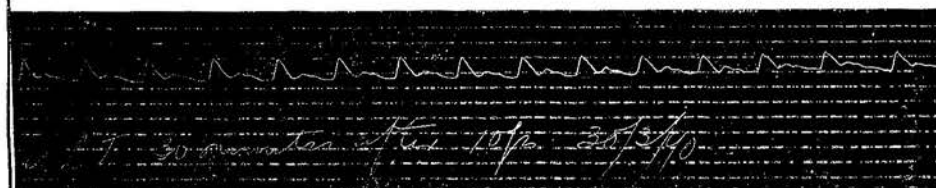


after 10 ppm of Quinine

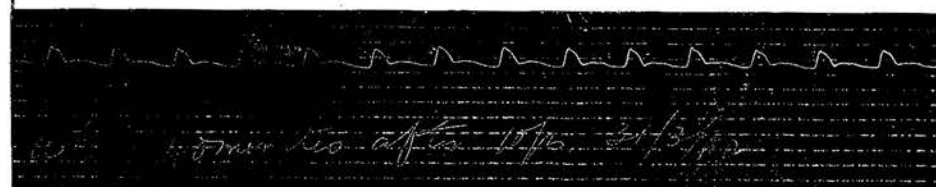
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"



"



"

