method of applying the remedy in hæmorrhage from that viscus. A sterile extract is not irritating, and may be used to wash out the bladder when bleeding occurs from that organ; it may also with advantage be added to the water used as a uterine douche in cases of *post-partum* hæmorrhage.

If we accept the theory that congenital hypoplasia of the vessel walls is associated with hæmophilia, we should not expect that in that pathological condition suprarenal extract would be followed by satisfactory results. In no single instance in which this condition has been treated with this drug have I been able to satisfy myself that benefit has accrued.

REFERENCE.

¹ *Journal of Physiology*, 1899.

MODE AND RAPIDITY OF REDUCTION OF
TEMPERATURE BY QUININE.

By WILLIAM SYKES, M.D., F.S.A.,
Torquay.

THE following three sets of observations on the mode and rapidity of action of quinine as an antipyretic when administered in cases of high temperature in a single large dose, as recommended by Liebermeister, were made by the writer some time ago, and were intended to form part of a series of observations on the action of antipyretics in cases of pyrexia. Circumstances, however, prevented their completion. As, however, they add a little to our knowledge of the clinical action of this class of drugs, I venture to publish them here.

The first case was that of a young man, aged 26, suffering from an attack of enteric fever. The observation was taken on the twelfth day of the disease (approximately). His temperature at 9 P.M. was 103.6°, pulse 100, respirations 24. At that hour I administered 30 grains of quinine sulphate in milk. I then fixed an old-fashioned sensitive clinical thermometer, without index, in the left axilla, and, sitting in the room, made frequent observations of the temperature of the patient, as recorded in the following table, in which Column I indicates the exact moment at which the observation was made; Column II the length of time elapsing between each observation; Column III the actual temperature recorded; and Column IV the reduction of temperature between each observation in tenths of a degree Fahrenheit.

CASE I.

I.	II.	III.	IV.	Remarks.
P.M.	Minutes.	Fahr.		
9.0	—	103.6°	—	Quinine sulph. gr. xxx.
9.17	17	103.6°	0.0	
9.49	32	103.4°	0.2	
10.1	12	103.3°	0.1	
10.4	3	103.2°	0.1	
10.14	10	103.1°	0.1	
10.18½	4½	103.0°	0.1	
10.25	6½	102.9°	0.1	
10.35	10	102.9°	0.0	
10.40	5	102.9°	0.0	
10.44	4	102.8°	0.1	From 10.25 to 10.40—that is, 15 minutes—the temperature was stationary, and then commenced to descend again.
10.53	9	102.7°	0.1	
11.0	7	102.6°	0.1	
11.3	3	102.4°	0.2	
11.4½	1½	102.3°	0.1	
11.7	3½	102.2°	0.1	
11.17	10	102.1°	0.1	
11.18½	1½	102.0°	0.2	

This series of observations, then, extended over 2 hours 18½ minutes, during which time the temperature fell 1.6° F. Deducting the first 17 minutes during which the temperature remained unaltered, the average rate of fall was 0.1° during every 7.59 minutes. The rate of fall, however, was not regular, but varied greatly, sometimes requiring as long as 10 minutes (once 12 minutes) to accomplish a drop of 1°, sometimes performing it in 1½ minutes, and once remaining quite stationary for 15 minutes. The fall of temperature was accompanied by profuse diaphoresis. At the conclusion of the observations the temperature was 102°; the respirations

26, and the pulse 92, and markedly dicrotic. The temperature, as stated, having thus fallen 1.6°, the respirations quickened 2 in each minute, and the pulse slowed 8 beats per minute.

The second series of observations were made two evenings later on the same patient. At 7.50 P.M. I administered 40 grains of quinine sulphate in milk. The temperature was then 104.4° F., the pulse 96, the respirations 34. The resulting decrease of temperature is recorded in the following table, in which the reference numbers are as before:

CASE I.—Second Series of Observations.

I.	II.	III.	IV.	Remarks.
P.M.	Minutes.	Fahr.		
7.50	—	104.4°	—	Quinine sulph. gr. xl.
8.10	20	104.3°	0.1	Rise of temperature.
8.30	20	104.38°	+0.05	
8.35	5	104.4°	+0.05	
8.42	7	104.33°	0.025	The temperature remained stationary from 9.35 to 9.55 (that is, for 20 minutes). From 10.8 to 10.18 the temperature was stationary; (that is, for 10 minutes), and again from 10.25 to 10.35 (a second period of 10 minutes).
8.50	8	104.24°	0.15	
8.57	7	104.2°	0.025	
9.5	8	104.14°	0.075	
9.15	10	104.1°	0.025	
9.20	5	104.0°	0.1	
9.30	10	103.7°	0.3	
9.35	5	103.6°	0.1	
9.45	10	103.6°	0.0	
9.55	10	103.6°	0.0	
10.0	5	103.5°	0.1	
10.8	8	103.2°	0.3	
10.18	10	103.2°	0.0	
10.25	7	102.9°	0.3	
10.35	10	102.9°	0.0	
10.40	5	102.7°	0.2	
10.50	10	102.4°	0.3	

The period occupied by this second series of observations was three hours, during which the temperature was reduced 2° F. As the temperature fell 0.1° during the first 20 minutes' observations, it is not safe to deduct anything, as in the previous instance, for this initial period, in calculating the rate of fall, which was in this series 0.1° for every 9 minutes. At the conclusion of these observations the temperature, as stated, was reduced to 102.4° F. The respirations (which in the middle of the period under consideration took on a marked Cheyne-Stokes character) to 32, and the pulse to 94 per minute, the temperature having thus decreased 2° F., the number of the respirations and of the pulse beats two each to the minute.

In this instance the rate of fall of temperature was, as in the last, markedly uneven, and there were no less than three periods of respectively 20 minutes, 10 minutes, and 10 minutes each, during which the fall of temperature was entirely suspended.

The third and last series of observations were made in the case of a child of 6 years of age, also suffering from enteric fever. At 8.10 P.M. of the fourteenth day of the disease the temperature was 104.1°, and 20 grains of quinine sulphate were administered, as before, suspended in milk.

I.	II.	III.	IV.	Remarks.
P.M.	Minutes.	Fahr.		
8.10	—	104.1°	—	Quinine sulph. gr. xx.
8.25	15	104.2°	+0.1	Rise of 0.1°.
8.32	7	104.0°	0.2	Rise of 0.1°. Rise of 0.2°.
8.50	18	104.1°	+0.1	
8.55	5	104.3°	+0.2	
9.0	5	104.3°	0.0	During a period of 5 minutes the temperature was stationary.
9.17	17	103.9°	0.4	
9.22	5	103.8°	0.1	
9.25	3	103.7°	0.1	
9.30	5	104.0°	+0.3	
9.33	3	103.6°	0.4	
9.37	4	103.5°	0.1	
9.40	3	103.4°	0.1	
9.43	3	103.3°	0.1	
9.45	2	103.1°	0.2	
9.50	5	103.0°	0.1	Rise of 0.3°.
9.55	5	102.9°	0.1	
10.0	5	102.8°	0.1	
10.15	15	102.5°	0.3	

The period over which this last series of observations extended was 2 hours 15 minutes, during which the total reduc-

tion of temperature was 1.7° F. Deducting the first 15 minutes of the period of observation (during which the temperature was not only unreduced, but even continued to rise) the rate of fall was at the rate of 0.1° for every 7.05 minutes occupied.

Here the rate of fall was even more irregular than in the preceding two series; during two periods of respectively 10 minutes and 5 minutes the temperature actually increased (although the subsequent fall was almost to the point which would have been attained had the intercurrent rise not occurred), and there was a stationary period of 5 minutes. During the last half-hour of the observation the rate of fall was very regular indeed, being at the rate of 0.1° during every 5 minutes.

We note:

1. The rapidity of absorption of the quinine, although only given as a powder suspended in milk. In the first series of observations, the temperature began to fall within 49 minutes, probably in a shorter time; in the second series within 20 minutes, and in the third series within 22 minutes. So that Liebermeister's statement that "the decline of temperature usually begins a few hours after taking the medicine" is decidedly an overstatement of the time occupied in producing a commencement of fall of temperature.

2. The size of dose, within certain limits, does not seem to affect the rapidity of the defervescence. In the preceding cases, we have respectively doses of 20 grains, of 40 grains, and of 20 grains administered with average result in the respective instances of 0.1° decrease for every 7.59 minutes, for every 9 minutes, and for every 7.05 minutes. The mean of the three series giving a result of 0.1° decrease of temperature for every 7.88 minutes occupied by the experiment.

3. There are four methods in which the antipyretic effects of the quinine might be thought to act: (a) By a destruction of pathogenic bacteria; (b) by a neutralisation of their resulting toxins; (c) by an interference with the heat-regulating centres; and (d) by producing diaphoresis. The destruction of pathogenic bacteria is negatived by the fact of the merely temporary nature of the defervescence which follows the administration of quinine. A destruction of bacteria would produce a permanent curative defervescence, not a merely temporary one. Moreover, we have no experimental proofs that a diluted solution of quinine of the strength of 20 or 30 grains of the drug dissolved in a bulk of fluid equal in volume to the whole of the blood of an individual, would exercise a particularly lethal effect on Eberth's bacillus. It is highly improbable that quinine in whatever strength would neutralise the chemical products of the typhoid bacillus, since they appear to bear no chemical relation to each other. There remain, therefore, only the two probable methods of action—on the heat centres and on the sweat centres. It seems improbable, if the heat-centre theory be true, and if my observations are, as I believe them to be, accurate, that the proportional rate of decrease of temperature after exhibition of the drug should be so irregular as it is, and that its speed should not be affected by the amount of dosage. A drug acting directly on a nerve centre might be expected to produce an immediately great and regular effect on its function which would be expected to agree in rapidity of action with the size of the dose administered.

If, however, we accept the last or diaphoretic theory of defervescence when produced by antipyretic remedies, it would explain many of the difficulties of the question. Since defervescence by diaphoresis depends upon the sweating itself and not upon its causation, it is obvious that the size of the dose of the drug administered, so long as it was sufficient to produce perspiration at all, would have no effect on the speed of the resulting defervescence. Since slight movements in bed by which the surface became chilled would temporarily stop the diaphoresis, the stationary and even regressive intervals during the period of falling temperature would be quite explicable on such grounds. Moreover, most, if not all, of the antipyretic group possess one quality in common, when administered for reduction of temperature in efficient doses: they produce violent diaphoresis, which also occurs in the night sweats produced by the toxins of the tubercle bacilli, which are in like manner succeeded by a normal or sub-normal temperature.

REFERENCE.

1 H. von Ziemssen, *Cyclop. of Med.*, i, 214.

THE BROMIDE SLEEP IN A CASE OF MANIA.

By PHILIP M. RAGG, M.B., C.M.,
Kingston, Jamaica.

I LATELY attended, in private practice a case of mania in which resort to the bromide treatment, as advocated by Dr. Neil Macleod,¹ gave excellent results.

The patient, a young Englishman, had been for eight hours in a state of alternating exaltation and depression when I was first summoned, the exciting cause being domestic and pecuniary worries of no great magnitude. He had taken at one dose forty 2-gr. quinine pills, with the avowed intention of committing suicide. Profuse sweating, headache, nausea, and prostration, with a temporary mitral systolic murmur resulted; and, though in a state of great mental excitation, his physical discomfort rendered him at first very amenable to treatment. For the first four days 20 grs. of sulphonal with 30 grs. of ammonium bromide were administered every twelve hours. After each dose he slept for some hours (as much as eight on the second night), but with incessant movements of the limbs and changes of position. He ate heartily, but in the intervals the mental exaltation increased, and he suffered from restlessness and delusions that made him difficult to manage. Thus on the third day, after a four and a-half hours' sleep, during the absence of the one available trained nurse, he gave his watchers the slip, and I arrived just in time to intercept him in the street, 100 yards from home, in a state of great excitement, staggering like a drunken man, singing at the top of his voice, and accosting passers-by.

On the fourth evening he attacked me furiously under the delusion that I was robbing him of his wife, to whom he is much devoted, when I sent her exhausted to rest in an adjoining room. On the fifth day, being anxious to keep him, if possible, out of the asylum, and after consultation with the medical superintendent of the institution, I determined to try the effect of the bromide treatment. In order to allow the effects of the sulphonal (last administered at 1 A.M.) to pass off, the new treatment was not commenced till 4 P.M., when he was again in a state of great exaltation, talking incessantly, with bursts of maniacal laughter. Potassium bromide in 2-drachm doses was then given at 4, 6, and 8 P.M., followed in each case by a tumbler of milk. At 9.15 P.M. he was apparently in a deep sleep, but as preparations were being quietly made for his wife's return to the next room for the night, he got up in bed, and with many invectives threatened to "do for me." He fought furiously for about thirty seconds, and then fell back exhausted. On assurances being given that she should remain in the room he became tractable, but a quarter of an hour later tried to follow me downstairs to "square me in the open." At 10 P.M. 3 drachms of potassium bromide were given, and after an hour's incessant talking, in which he was profane and witty by turns, and extravagantly lauded his wife's personal charms, he got eight hours' sleep.

On the sixth day the potassium bromide was given, in 2-drachm doses, at 8 and 10 A.M. and 12, 2, and 4 P.M., followed in each case by a tumbler of milk, giving a total of 10 drachms of bromide in the twenty-four hours. The early administration was due to his refusing to remain in bed and being intractable in the morning. From 10 A.M. onwards he slept soundly, and required some rousing for the two-hourly draughts. There was slight difficulty in swallowing, but he drank from a tumbler and assisted in holding it. He got up without suggestion during the day to obey the calls of Nature. At 6 and 8 P.M., after being roused to take milk, he became restless and loquacious.

On the seventh day, having had fairly deep sleep through the night, at 5.30 A.M. he got out of bed to pass water, then fell into deeper sleep, which continued throughout the day with little muscular movement. He lay with eyes half open and glazed, mouth wide open, breathing somewhat stertorously. He was roused every two hours to take milk; he recognised those who gave it, always looked across to his wife, smiled, spoke affectionately in a thick voice, and went off at once to sleep. His tongue was covered with a thick white fur, and his temperature was normal throughout the progress of the case. At 4 P.M., when his wife was speaking to me at the door, though apparently in profound sleep, he roused himself—suspicious, as always when she moved—swore violently at me for my "intention of removing her," struggled hard for a few moments, and, quickly exhausted, went off to sleep again.

During the whole of the eighth day he slept profoundly, even more so than on the seventh. His face was pallid and somewhat leaden in hue; he took milk as before, but with more difficulty in swallowing, so that on three occasions he was fed with a spoon. He got out of bed once to follow his wife when she left the room; however deep his sleep, he seemed to wake instinctively if she left him.

On the ninth day he had deep but more natural sleep.

On the tenth day, having slept well all night, he was easily roused, and took a light breakfast with relish, but he had difficulty in swallowing. He slept the greater part of the day and was always drowsy. There was no extravagant behaviour whatever except insisting on kissing the nurse, and he allowed his wife to leave the room at intervals without suspicion or demur.

On the eleventh day, after a good night, he was rational and very amenable to treatment. He was extremely weak, but walked with assistance round the room, when he was content to go back to bed for the rest of the day, feeling "tired." He slept most of the day.

On the twelfth day he left the bedroom for the first time, and shaved himself well. His tongue was still very foul. His mental state had returned practically to his normal, which is that of a restless, excitable, and rather self-willed individual. From this time onwards there has been a steady return of physical strength, and he has been rational in his behaviour, but easily affected to tears for the first few days by a sense of his inability to work, by acts of kindness, and occasionally when not allowed to act on his own judgment.

In the treatment of this case the drug was not pushed to the extent advocated by Dr. Neil Macleod, as after a twenty-