THE VALUE OF QUININE UREA IN THE TREATMENT OF PNEUMONIA.

BY

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INTRODUCTION.

Since the year 1911 several observers, notably in Sweden, Holland, Germany and more especially America, have published numerous articles on the action of quinine in pneumonia. It is remarkable that a form of treatment for which large claims are made elsewhere has received so little attention in this country: Gibson in praise of the treatment of pneumonia with quinine and Sir Almroth Wright, who condemns the use of ethylhydrocuprein hydrochloride - optochin or Morgenroth's drug - in pneumonia, are noteworthy exceptions.

Professor W. E. Dixon referred to the treatment of pneumonia with ethylhydrocuprein hydrochloride, in a discussion, at the annual meeting of the British Medical Association at Cambridge in 1920. He said that it was difficult to explain why physicians had not obtained more striking results with a drug, which, administered in therapeutic doses, destroys the primary cause of the disease.

In view of the many interesting observations in the literature and favourable statements by clinicians, who have used preparations of quinine other than ethyl-hydrocuprein hydrochloride, it would appear desirable to carry out a series of observations upon the action of quinine urea - quinine and urea hydrochloride - in lobar and lobular pneumonia. The object of this paper is to

illustrate with a series of cases the value of quinine as a therapeutic agent in pneumonia and to discuss, in the light of facts already ascertained, the prospect of further research into its mode of action.

REVIEW OF LITERATURE.

In the year 1875 Schultz (1), of Mount Vernon, Indiana, had under observation two hundred and thirty-eight cases of lobar pneumonia. The cases presented the toxic symptoms associated with a virulent infection. Schultz treated all his patients with quinine and was impressed with the favourable results: he said 'How quinia accomplishes good results .... has not yet been determined. I opine that it is not by its fever-lowering property, for I have seen the general condition .... improved even when no impression was made on the temperature. .. There seems to be inherent in quinia, when given in large doses, a specific power of so influencing diseases attended with great and rapid tissue metamorphosis and retention of the waste-products of such tissue changes in the system that the diseases take on a more favourable course and come to a more happy issue under its use.'

It was not, however, until the year 1904 that a

systematic attempt was made to treat pneumonia with quinine. In that year Galbraith (2) revived the treatment of pneumonia by quinine in massive doses, and it was this that led Solis Cohen to employ it at the Philadelphia General Hospital. For his experiments he used quinine urea which he administered by hypodermic injection. The initial dose was fifteen to twenty-five grains followed in three to four hours by a second injection and perhaps by a third and even a fourth injection some time within the first twenty four hours according to results. Occasionally it was thought desirable to continue with large doses on the second and third day, followed by smaller doses by the mouth. Some cases must have received more than four drachms of quinine urea in three days yet quinine poisoning did not occur.

In the year 1911 Solis Cohen (3) published the results of his observations made upon a large number of cases and extending over a period of several years. He found that the temperature and pulse rate fell gradually and proportionately. The respiration rate fell more rapidly, with a tendency to restitution of the normal pulse-respiration ratio. The blood pressure, which sometimes fell after the injection, soon returned to the former or a higher level. The structural pathological processes evolved in the customary manner apparently unmodified by the treatment. The termination was by lysis at about the ordinary time: crisis did not occur. The complete clinical picture was thus favourably changed.

He says 'The most striking results of the large doses of quinine urea are thus functional; and since the most significant features are relief of respiration and the maintenance of normal cardiac vigor and blood pressure, it seems logical to infer that the effect is chemical and antitoxic. This view is further borne out by the absence of quinine intoxication, suggesting a mutual neutralization of disease-poison and drug.' He considered that the urea radicle might be a chemical sensitizer, or linking body; or that it might delay the excretion of the quinine.

In May of the same year - 1911 - Gibson (4), addressing the Eastern Medical Society of Glasgow on lobar pneumonia said 'In cases where there is severe toxaemia and great leucocytisis much may be done by the employment of quinine. In several instances of this kind - in which the patients had even reached a stage of profound coma, with complete relaxation of the sphincters and every evidence of imminent danger - the hypodermic use of quinine has produced the most remarkable effects. The best preparation for this purpose is the acid hydrochloride, which is extremely soluble and which may be administered hypodermically in doses of two grains every two hours, or every hour. No more gratifying results have ever occurred in my own hands than from this method of treatment."

It was not until six years later that further reference was made to the action of quinine-urea in pneumonia; during these intervening years, however, much interesting work was reported on the action of ethylhydrocuprein hydrochloride in relation to pneumonia.

Morganroth and Levy (5) experimented with ethylhydrocuprein hydrochloride on mice inoculated with cultures of pneumococcus. They found that the drug possessed marked prophylactic and therapeutic value; when administered before inoculation it prevented the development of infection in nearly every case, while when it was administered after inoculation half the cases were cured. Every untreated mouse died.

Sir Almroth Wright (6) investigated Murgenroth's discovery with a view to ascertaining whether ethylhydrocuprein hydrochloride might have any therapeutic value in the pneumonias of man. He established the fact that this drug has a specific bactericidal effect on the pneumococcus in vitro and in vivo. Bactericidal experiments were conducted in vitro on the blood fluids and urine of untreated mice and mice receiving the same dose of ethylhydrocuprein hydrochloride as Morgenroth employed in his experiments. The serum and urine of those that received the drug were found to be strongly penumococcicidal, and this power was not diminished by heating to 60° C. Further experiments, carried out in part on normal men and in part on pneumonia patients, showed that the blood of man is also rendered bactericidal to the pneumococcus by the administration of ethylhydrocuprein hydrochloride. The opsonic power of the serum is not appreciably affected. It was sound found, however, that the drug did not conform to the idealof being poisonous for the pneumococcus and non-poisonous for the more special tissues of the patient. Of

Of twenty-one pneumonia patients, treated by Frankel, three developed amblyopia, and in a further series of eight cases, treated by Sir Almroth Wright, there were two cases of amblyopia, one of which went on to amaurosis. The dose was 0.5 to 2 gm, daily. The treatment was therefore abandoned, and as there was insufficient material on which to base trustworthy comparative statistics it was decided not to draw conclusions from any one feature, such as the case-mortality, but to give attention to any significant clinical manifestation. There were no clinical manifestations in the cases under observation, and Sir Almroth Wright concluded that ethylhydrocuprein hydrochloride does not exert a favourable influence on human pneumonia. In connection with the inefficacy or practical inefficacy of the drug as a remedial agent in human pneumonia Sir Almroth Wright suggests two possible explanations.

(1) That the advantage, which one might expect to reap from the circumstance that a bactericidal power is conferred upon the blood fluids by ethylhydrocuprein hydrochloride, is neutralized by some other antibacterial property diminishing. Thus, although the opsonic power of the blood is apparently unaltered, he considered it possible that, as a result of some devitalising action of the drug on the phagocytes, the ingested microbes might not be destroyed.

(2) That in mice the pneumonic infection takes the form of a septicaemia and as a result the drug has free

access to the infecting organisms; whereas the tissue spaces in association with a consolidated lung are filled up with coagulated lymph and thus the influx of bacteriotropic substances from the blood is prevented.

It would seem desirable, at this point, to complete the references to ethylhydrocuprein hydrochloride, postponing for the time reference to quinine urea, although this will involve departure from precise chronological order.

In the year 1916 Moore and Chesney (7) reported the results of a series of experiments on the action of ethylhydrocuprein hydrochloride on the pneumococcus. These experiments confirmed the earlier work of Morgenroth and Sir Almroth Wright: its bactericidal action extends to the four main groups of pneumococcus and the serum of animals and man receiving the drug acquires an inhibitory and bactericidal power. The rabbit, however, presents an interesting exception to this rule. Weiss (8) demonstrated that the administration of various quinine derivatives - including ethylhydrocuprein hydrochloride - to the rabbit does not produce a pneumococcicidal action in its serum, but Solis Cohen (9) was able to protect rabbits with a dose of 0.01 gm. of ethylhydrocuprein hydrochloride per kiligram of body weight against fifty minimal lethal doses of pneumococcus given two hours later by intravenous injection - a dose, weight for weight, very much larger than is required to afford protection in mice.

The fact that the liver of the rabbit has a high destructive action on quinine alkaloids and that both leucocytes and red blood cells have a marked affinity for cinchona compounds is a possible explanation of why it is impossible to render the serum of the rabbit pneumococcicidal by administration of quinine derivatives.

A bactericidal action for the pneumococcus is secured in the blood stream of patients if they are given an amount of ethylhydrocuprein hydrochloride represented by .024 gm. per kilogram of body weight per twenty-four hours. (Chesney, (10).) The time of appearance of the bactericidal action in the serum is shortened and the possibility of invading bacteria becoming fast to the drug is less when the first dose is relatively large.

From October 1915 to May 1917 Moore and Chesney (11) gave an extended trial to this drug. Almost all the cases of lobar pneumonia admitted to the wards of the Hospital of the Rockefeller Institute during this period were treated with ethylhydrocuprein hydrochloride - cases due to pneumococcus type I did not receive the drug, but were treated with specific immune serum. The results were disappointing. In four per cent of the cases treated temporary impairment of vision had occurred and in one case permanent blindness. They attribute the failure to the fact that the toxicity of ethylhydrocuprein hydrochloride was such as to keep

the limit of dosage below the limit of effectiveness: a concentration of about one in five-hundred thousand, which is as much as may safely be attained in the blood stream of the patient, is not sufficient to penetrate the alveolar exudate to any marked degree. The pericardial fluid, obtained post mortem, showed pneumococcicidal power, and the serum of one patient who received a very large dose was also pneumococcicidal.

Kolmer (12) was able to demonstrate that ethylhydrocuprein hydrochloride by subcutaneous injection in doses without protective value, usually increases the protective value of antipneumococcus serum type I in a slight but definite manner in sever infections of mice and rats with homologous pneumococci.

Solis Cohen (13) has confirmed these observations in connection with a more general consideration of most of the quinine derivatives in relation to pneumonia. Amongst the quinine derivatives tested were quinine urea ethylhydrocuprein hydrochloride, quinine bisulphate and quinine hydrobromide. All were found to exert a high bactericidal power on pneumococcus in vitro, and that this action was a specific one was shown by cross bactericidal tests - employing on the one hand quinine derivative with cultures of B. typhosus and of a staphylococcus, and on the other hand arsenobenzol, phenol, mercuric chloride, and sodium salicylate with cultures of pneumococcus.

Thus the value of ethylhydrocuprein hydrochloride,

the most active as a bactericide, was from two-hundred to four-hundred times greater for the pneumococcus than for B: typhosus and the staphylococcus. The various quinine derivatives however differed markedly in their relative pneumococcicidal power and quinine urea was found to be one of the weakest in this respect (Cohen (14).) Their protective power against virulent infections of pneumococcus in mice and rabbits also varied and again quinine urea was the least potent. The protection is greater when the drug is given intravenously than intramuscularly, and in the case of quinine urea it is most marked when repeated injections are given, when it has a marked curative value. Solis Cohen lays stress on the prolongation of life in infected mice receiving repeated injections of non-toxic doses of quinine urea- or ethylhydrocuprein hydrochloride -, and says 'For such prolongation in man gives time for the development of the natural immunity which is manifested by critical recovery in untreated cases and by gradual defervescence in cases treated with quinine.'

An investigation into the action of these various quinine derivatives on phagocytosis revealed the fact that, in high dilution, they accelerate the phagocytosis of pneumococci by rabbit leucocytes while low dilutions retard phagocytosis and induce degenerative changes in the leucocytes. It was also found that, injected intra-muscularly into rabbits, they increase the phagocytic power of the rabbit sera for

pneumococci. ... These results are in accord with clinical observations. Solis Cohen says, - 'Contrary to expectation, the administration of quinine in any form and by any method to a patient in the early stages of a lobar or lobular pneumonia not only does not reduce the numbers or the apparent activity of the leucocytes, but - so far as one may judge in an infection normally accompanied with a progressive increase in the white-cell count - actually seems to increase them.'

In clinical studies of the beneficial influence of quinine salts in the pneumonias of man Solis Cohen (15) observed three outstanding facts: 1. The relief of toxic symptoms without appreciable influence on the evolution of physical signs, 2, the change of termination from crisis to lysis and 3, the absence of quinine poisoning, even when enormous doses are given - this does not apply to ethylhydrocuprein hydrochloride however. He says, 'There is nothing in the known pharmacologic influence of quinine as a function modifier that will account for either the first or the second of these facts. Nor can bactericidal action alone explain them. The third fact indicates the presence of a quinine-tolerance in the subjects of pneumonia.' It appeared that there might be a mutual antagonization or inhibition, physical or chemical, direct or indirect, of quinine by the pneumonia poison-complex, and of the pneumonia poison-complex by quinine.

The following experiments were undertaken by Solis Cohen, Weiss and Kolmer in the hope that they might throw light on the problem. While admitting that the finding of the poison or poisons in question should logically precede such investigation it was deemed practicable to pursue the two lines of research together, partly in the hope that one might throw light on the other; and partly that at least certain preliminary questions as to the possible action of quinine might be determined. They experienced great difficulty in demonstrating an endocellular toxin in the pneumococcus, and were unable to produce uniformly a toxin which was hemolytic and also produced anaphylaxis on primary intravenous injection in guinea-pigs. The organism used was Type I pneumococcus, and it was transplanted every other day and from time to time passed through a mouse in order to maintain the M.L.D. for mice (24 hours) at 0.000,000,1 c.c. of a twenty four hour broth culture. Elaborate precautions were taken in the preparation of the pneumotoxin and its toxicity was tested by intravenous injections in guinea-pigs and white mice, and by intra-peritoneal injection in white mice. Having established the lethal dose of each preparation of pneumotoxin, attempts were made to neutralize its toxicity by means of the various quinine derivatives.

In the first experiment the toxin and drug were mixed in the test tube in proper proportions and, after

a period of incubation at room temperature, injected intravenously into a guinea-pig. This method was abandoned however as it was found that the quinine was precipitated. In the second experiment the proper dose of the drug was injected into the animal two hours before the injection of 2 M.L.D. of the toxin: the animals all died. An attempt was then made to study the effect of repeated injections of sublethal doses of pneumotoxin followed by a corresponding dose of quinine salt. This experiment, representing more closely the conditions which obtain when the drug is exhibited to a pneumonia patient, had to be abandoned because of the extreme lability and rapid deterioration of the pneumotoxin. A fourth experiment showed that quinine salts exert no inhibition on the hemolytic activity of pneumotoxin. In fact the reverse phenomenon was observed: there was a summation of hemolytic powers.

From human lung tissue in the stage of grey hepatization, obtained post mortem, Solis Cohen was able to prepare a highly toxic extract producing anaphylactic-like symptoms in guinea-pigs and rabbits. Attempts to neutralize this lung toxin with quinine derivatives gave inconstant results. Thus it was found that while quinine hydrochloride, quinine urea and ethylhydrocuprein hydrochloride gave little or no protection, quinine hydrobromide exerted a marked neutralizing action on the toxicity of the pneumonic lung extract, prolonging the life of the animal up to

five days or more after the injection of 1 M.L.D.

The pneumonic lung extract was found to be strongly hemolytic, and attempts to neutralize its hemolytic power with quinine derivatives gave somewhat paradoxical results; thus ethylhydrocuprein hydrochloride, quinine and quinine urea gave a slight inhibition when large doses were used, while quinine hydrochloride, quinine hydrobromide and quinine bisulphate behaved in a reverse way, giving marked inhibition in nonlytic doses and no inhibition in lytic doses.

Attacking the problem from another angle attempts were made to ascertain whether or not the pneumococcus protein or substances present in the blood of pneumonia patients would exert a neutralizing influence in quinine poisoning. The experiments were barren of result.

A detailed record of these experiments, briefly referred to above, concludes, - 'Neither the clinically beneficial action of cinchona derivatives in the pneumonias nor the increased tolerance of pneumonia patients receives elucidation from the experiments reported; the results being largely negative. Certain suggestive phenomena were observed that further study may elucidate. That cinchona derivatives are specifically pneumococcicidal and that they increase phagocytic activity has been shown in previous papers. Whether their influence on general metabolism and in general

antibody production will suffice to explain their further protective and curative influence remains to be determined.'

Solis Cohen (16) considers quinine the pharmacodynamic centre in the treatment of pneumonia, and postpituitary and digitalis as the principal pharmacodynamic aids. He says, 'I have found no other agents equal to them, except, within limitations, the specific type I serum in type I cases and mixed (polyvalent) pneumonia bacterins in other cases.' Nice (17) also reports favourably on the action of quinine in pneumonia. Solis Cohen does not employ quinine for the purpose of reducing temperature, but to combat bacteria, bacterial poisons and tissue poisons. The reduction of temperature is an incident of its action and affords a guide for dosage, both as to quantity and frequency. Commonly, he says, the temperature, if above 102 f. is brougt to or below that figure within three or four hours after the administration of the drug in sufficient quantity, while a persistent tendency to reascend is the indication for continuing or increasing the medication. As a rule cases which did not respond were found, post mortem, to have extensive plural or pulmonary suppuration. Solis Cohen considers quinine hydrobromide the preferable salt of quinine for administration by mouth, and for intramuscular injection either of these or the dihydrochloride. He advocates massive dosage and says 'I have not myself encountered any instance of untoward cinchonism .. in

this respect the unmodified quinine molecule differs very much from ~~the~~ ethylhydrocuprein hydrochloride, whose toxicity is so great as to render it unsafe for internal use. Even in cases of quinine idiosyncrasy it will be found that quinine in large doses is well tolerated during the progress of an acute lobar pneumonia.' He recommends as an initial dose by the mouth twenty-five to thirty-five grains, and intramuscularly twenty to twenty-five grains, followed in either case by smaller doses at three to four hour intervals. For intravenous injection ten to fifteen grains in 100 c.c. of physiologic sodium chloride solution is advised: one dose by the intravenous route will usually be found sufficient.

A review of the literature on this subject would not be complete without reference to Professor W. E. Dixon's (18) observations on quinine and its related alkaloids in pharmacology and therapeutics. He says, - 'Quinine is peculiar among alkaloids in that it has no very definite specific action on any particular tissue in the body. Its action on all living tissues is to cause diminished activity and diminished metabolic changes. Sometimes there is a transcient increase of activity before the depression is evident ... The spirochaetes of vegetable decomposition become motionless in the presence of quinine in strength of one in ten-thousand ..... similar concentrations of quinine in the blood act on the white blood cells in

the same way .... movements cease and the corpuscle becomes granular. Quinine, then, should have the power to limit inflammatory processes, for it prevents the migration of white blood cells, and it is possible that the internal administration of large doses of quinine may limit pus formation.' He observed that the action of quinine is not confined to intact protoplasm but extends to the ferments, some of which act better in very dilute solutions; while traces of quinine in the blood inhibits acid formation. Referring to the specific pneumococcicidal power of ethylhydrocuprein hydrochloride he says - 'It is not easy to explain why physicians have not obtained more striking results with a drug which destroys the primary cause of the disease. It is of comparatively little value to administer tetanus antitoxin when the toxin has already poisoned the nerve cells, and I venture to suggest that for a similar reason ethylhydrocuprein hydrochloride may be of little value when the pneumonic condition is at its height. The pathology of early pneumonia is not well known, but the pneumococcus is apparently plentiful only in the early stages of the attack. The inflammatory process then continues in the ordinary course and may go on, even though all the pneumococci be dead. If this interpretation is correct ethylhydrocuprein hydrochloride would be of little value in the treatment of well pronounced cases of pneumonia, but should be of inestimable value in early cases and as a prophylactic. So certain are

we of our facts concerning this drug - that we can render the blood of our patients pneumococcicidal - that the gravest reasons only should condemn it to oblivion."

DESCRIPTION OF CASES.

At the Royal Naval Hospital, Chatham, during the autumn of 1917, I had an opportunity of treating several cases of lobar pneumonia with quinine urea. Professor Gulland mentioned the treatment of pneumonia, advocated by Solis Cohen, in his lectures on medicine at the University of Edinburgh in 1916-17; and with Professor Gulland's observations as a guide I experimented on those cases of pneumonia which came under my care. At first I administered quinine urea by hypodermic injection in concentrated solution, but soon abandoned this practice as I found it was not infrequently followed by necrosis at the site of injection. The areas of necrosis varied from the size of a pea to an inch or more in diameter, but in no case did the skin give way over one of these necrotic areas; and apart from the grey discolouration of the skin over the subadjacent necrotic tissue - in one case it was

still evident two months after the injection - I observed no ill effects. Latterly I have been able to arrange with Messrs. Parke, Davis & Co., for a supply of five c.c. ampules each ampule containing a solution of quinine urea in the strength of one grain in one c.c. This is a convenient dilution for intramuscular injection and no ill effects have followed its use.

No records are avilable of the cases of pneumonia which I treated with quinine urea in the Royal Naval Hospital, Chatham. These cases were in the nature of a preliminary investigation; but the results were sufficiently encouraging to persuade me to continue this form of treatment. The cases which I describe occurred, during the last two years, in the course of general practice in the New Forest.

CASE I.

J.B., a woman, aged 29; good personal and family history, and of an exceptionally robust type, complained of severe frontal headache and giddiness. When I saw her she had a temperature of 101.5°, pulse 110 and respirations 23, she had had a rigor two hours previously. There was no cough and I detected no modification of the breath sounds. Ten grains of Dovers powder failed to give her a good night's rest, she commenced a short dry cough, and had a second severe rigor in the early morning. When I saw her, about 5 a.m., she was more comfortable but during the day she

Patient's Name J.B., CASE I. Ward

MONTH — An injection of quinine urea is indicated thus: ↓. The size of dose in grains is represented by Roman numerals.

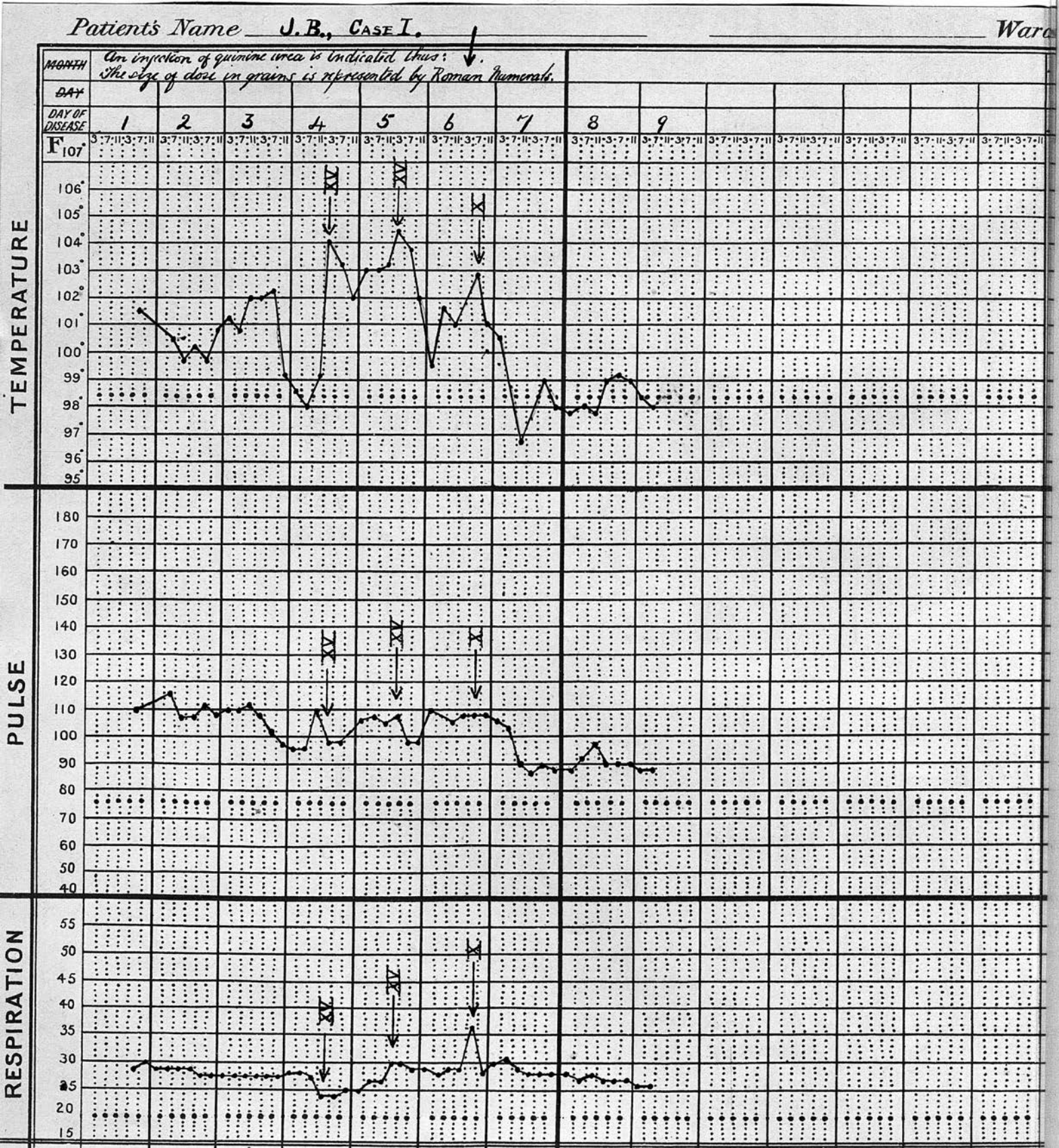
DAY

DAY OF DISEASE: 1 2 3 4 5 6 7 8 9

TEMPERATURE — F 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96° 95°

PULSE — 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

RESPIRATION — 55 50 45 40 35 30 25 20 15



got steadily worse and towards evening became delirious. There was now considerable dyspnoea, the cough was persistent and there were signs of a commencing patchy consolidation of the right lung. A drachm and a half of paraldehyde in brandy per rectum was followed by a short period of restless sleep, and the patient commenced the third day of the illness in an exhausted condition. At noon the temperature was 102, vomiting commenced and it became necessary to administer stimulants per rectum, at 12 p.m. the patient collapsed - the temperature fell to 98.6° and then to 97.6°, there was incontinence of urine and faeces. For twelve hours the patient lay in a semi-comatose condition, when the temperature rose rapidly to 104°, the pulse was weak and irregular, the breathing dyspnoeic and the whole clinical picture that of profound toxaemia. I had now obtained a supply of quinine urea and at once administered fifteen grains intramuscularly. Within half an hour the temperature fell to 102°, the patient perspired freely and was soon asleep. The following day - the fifth of the disease - the patient relapsed, toxic symptoms reasserted themselves, and she appeared in imminent danger. Dr. J. J. Perkins was called in consultation with Dr. Gurney Dixon and myself; there was evidence of spread of the disease to the left lung and the prognosis was grave. The temperature was now 104.4°; fortunately a second injection of fifteen grains of quinine urea was followed by marked relief of the toxic symptoms, the

Patients Name A.M., CASE 2. War

MONTH — An injection of quinine urea is indicated. Thus: ↓
DAY — The dose in grains is represented by Roman numerals.
DAY OF DISEASE: 1 2 3 4 5 6

TEMPERATURE
F 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96° 95°

PULSE
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

RESPIRATION
55 50 45 40 35 30 25 20 15

patient slept and the temperature fell to 99.6° without any symptoms of collapse. On the sixth day of the disease the temperature commenced to reascend, but the patient's general condition was more satisfactory, and the vomiting having ceased rectal feeding was discontinued.

At 8 p.m., the temperature had risen to 103.8° and I administered a third injection of ten grains of quinine urea. As in both previous occasions the injection was followed by relief of toxic symptoms; the patient progressed satisfactorily and further injections were not called for. There was some deafness and singing in the ears after the third injection; and convalescence was unduly prolonged owing to the development of phlebitis in the right leg.

CASE 2.

A.M., a woman, aged 21, good personal and family history and a robust type; complained of pain in her stomach and headache. On examination her temperature was 103°, pulse 130 and respirations 30. There was evidence of commencing consolidation of the right lower lobe. She was admitted to hospital on the second day of the illness; her temperature on admission was 104.4°, but her general condition was satisfactory and I decided to withhold the quinine urea. She experienced a restless night, however, and as her condition in the morning was less satisfactory I administered intramuscularly ten grains of quinine urea. Two hours later

Patient's Name M.B., CASE 3. Ward

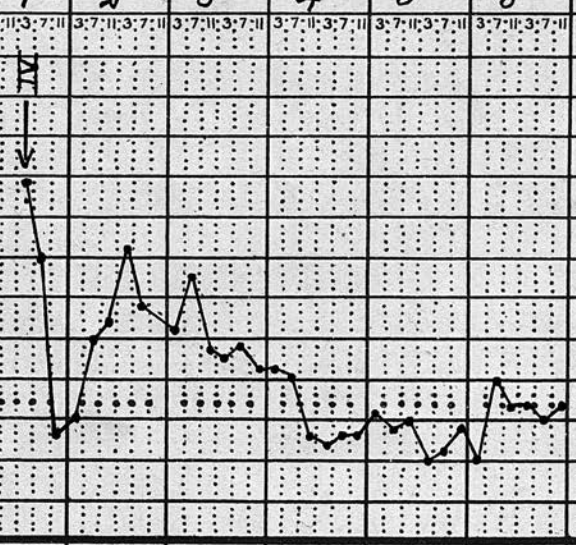
On injection of quinine urea is indicated thus: ↓ IV
The dose in grains is represented by Roman numerals.

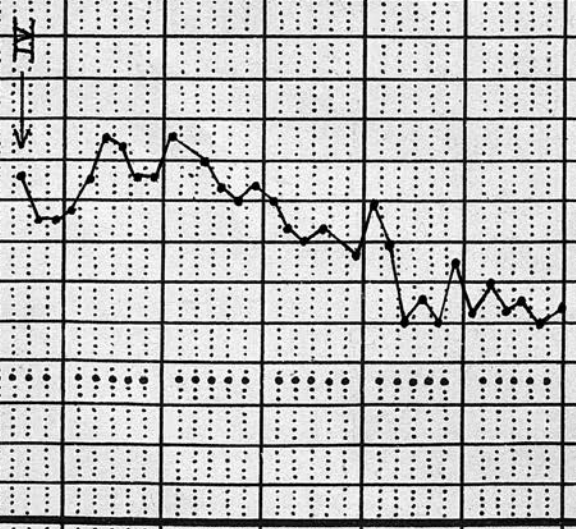
MONTH
~~DAY~~
DAY OF DISEASE 1 2 3 4 5 6

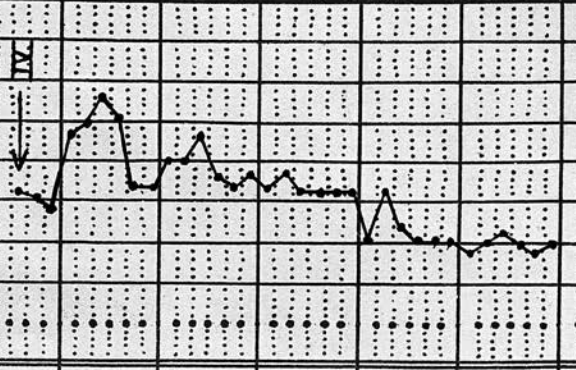
TEMPERATURE
F 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96° 95°

PULSE
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

RESPIRATION
55 50 45 40 35 30 25 20 15







her temperature had fallen to 102° and she slept for two hours. The temperature continued to fall until at 8 p.m. it was 99.2°. She had a comfortable night. The following day the sputum became rust coloured; the temperature continued below 100.5° and the termination was by lysis on the 5th day.

CASE 3.

M.B., a girl, aged 7, with a delicate constitution and showing some evidence of rickets, developed signs of a commencing consolidation of the right base while convalescing from chicken-pox. I administered four grains of quinine urea intramuscularly. The temperature dropped from 103.8° to 103° within half an hour of the injection and continued to fall; six hours later it was 97.8° and the child was sleeping quietly. Apart from the fact that her respiration and pulse rate continued high her appearance suggested that the disease had aborted. The following afternoon the temperature rose to 102.2°, and there were definite signs of consolidation onvolving the right base, but as her condition was satisfactory I did not repeat the dose of quinine urea. The temperature continued below 101.5° and the termination was by lysis on the fourth day.

CASE 4.

T.G., a boy, aged 18. This patient was an ill-nourished gipsy, brought in to hospital from his

Patient's Name T.G., CASE 4. War

An injection of quinine urea is indicated thus: ↓
The dose in grains is represented by Roman Numerals.

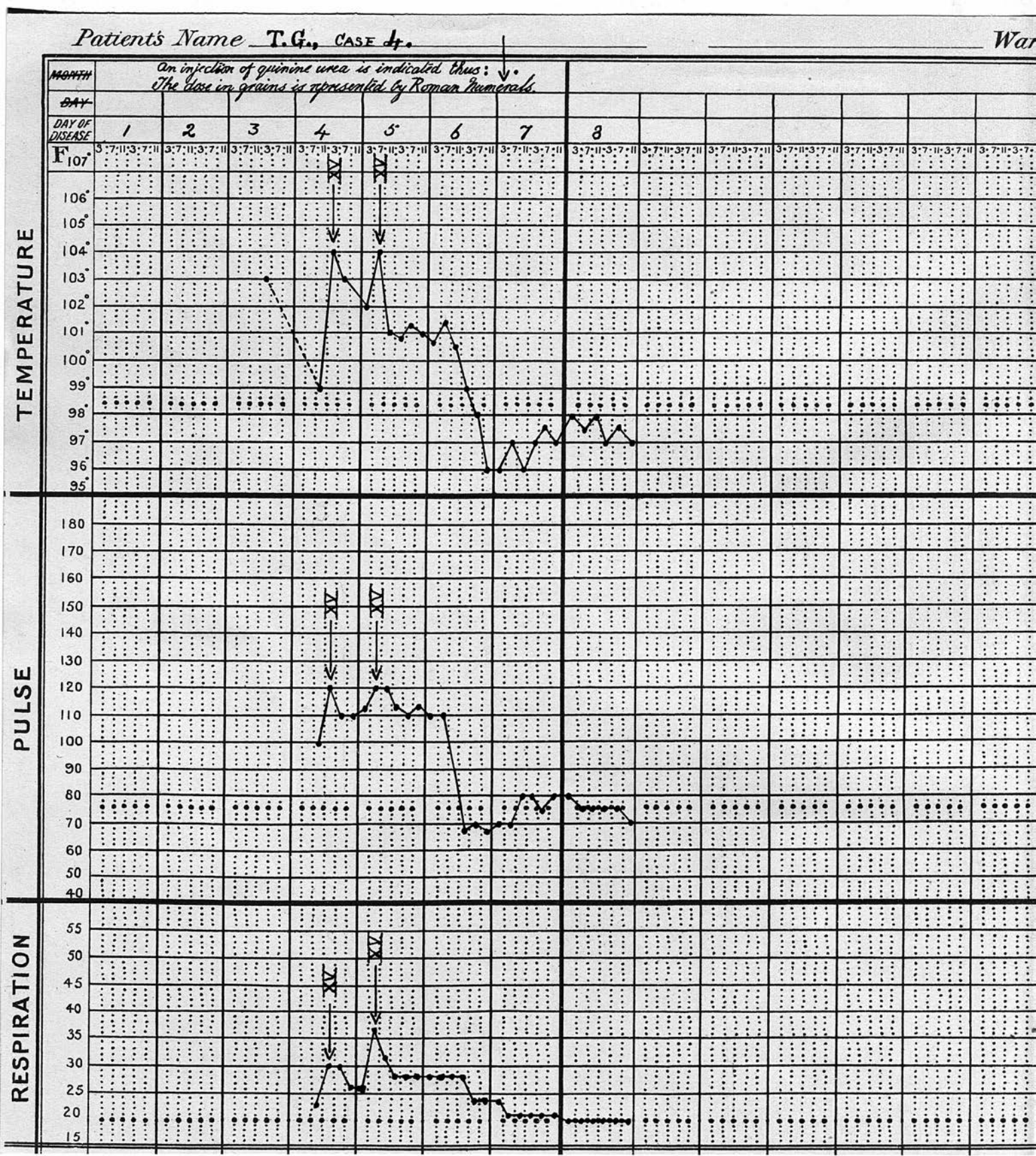
MONTH
DAY
DAY OF DISEASE 1 2 3 4 5 6 7 8

F 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96° 95°

TEMPERATURE

PULSE 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

RESPIRATION 55 50 45 40 35 30 25 20 15



tent in the New Forest, where he had been seen the previous day by the district nurse. The nurse reported that he complained of a pain in his chest, that his temperature was 103° and that he had a bad cough. It was difficult to obtain any history but it appeared that he had been ill for three days. On admission his face was cyanosed, his expression distressed, the tongue was dry and brown and there was extreme muscular prostration. He was got to bed and stimulants were administered, the temperature rising rapidly from 99° - on admission - to 104°, lethargy gave way to extreme restlessness and he became delirious. The pulse was irregular and easily compressible, the right heart was dilated and the abdomen distended and tympanetic. There were extensive patches of consolidation in both lungs. I administered 1.c.c. of posterior pituitary followed ten minutes later by fifteen grains of quinine urea. The patient responded to the injections, became less restless and the temperature fell gradually to 101.8°. At the same time his colour improved, he began to perspire and the pulse became stronger and more regular. He was no longer delirious but complained that he was very tired and wanted to sleep. Two drachms of paraldehyde with brandy per rectum were administered and he obtained several hours sleep during the night. The following day, however, he again became very restless, his colour and the character of his pulse were ominous, and I decided to give a further dose of

Patient's Name B.C., CASE 5. Ward

MONTH An injection of quinine urea is indicated thus: ↓VI
~~DAY~~ the dose in grains is represented by Roman numerals.

DAY OF DISEASE 1 2 3 4 5 6 7 8 9 10 11 12 13 14.

F 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96° 95°

TEMPERATURE

PULSE 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

RESPIRATION 55 50 45 40 35 30 25 20 15

quinine urea. The injection was followed with the fall in temperature and relief of toxic symptoms associated with the administration of quinine in these cases and the patient made an uninterrupted recovery.

CASE 5.

B.C., a woman, aged 73, with a history of 'winter-cough' of several years duration. She had aortic incompetence and mitral incompetence and there was considerable hypertrophy of the left ventricle. Organisms isolated from her sputum showed a preponderance of pneumococci, there was also micrococcus catarrhalis and a few staphylococci but no tubercle bacilli. She had had two series of inoculations of autogenous vaccine, at four months interval, followed on both occasions by a satisfactory period of relief from bronchial catarrh: and I contemplated a third series of inoculations when she developed an acute attack of bronchitis. Her temperature during the first week of the illness ranged along the 100° line, with early morning remissions of one degree or more. Her respirations were not unduly distressed, but the cough was troublesome and there was a small quantity of frothy sputum. She took nourishment well, but the condition of her heart gave cause for anxiety: an increasing dilitation of the left ventricle and an increasing pulse rate were ominous of commencing cardiac failure. Towards the end of the first week it became clear that the condition had become one of bronchopneumonia. The

Patient's Name J.M., CASE 6. Ward

MONTH

DAY

An injection of quinine urea is indicated thus: ↓
The dose in grains is represented by Roman Numerals.

DAY OF DISEASE: 5 6 7 8 9 10 11 12 13 14

TEMPERATURE

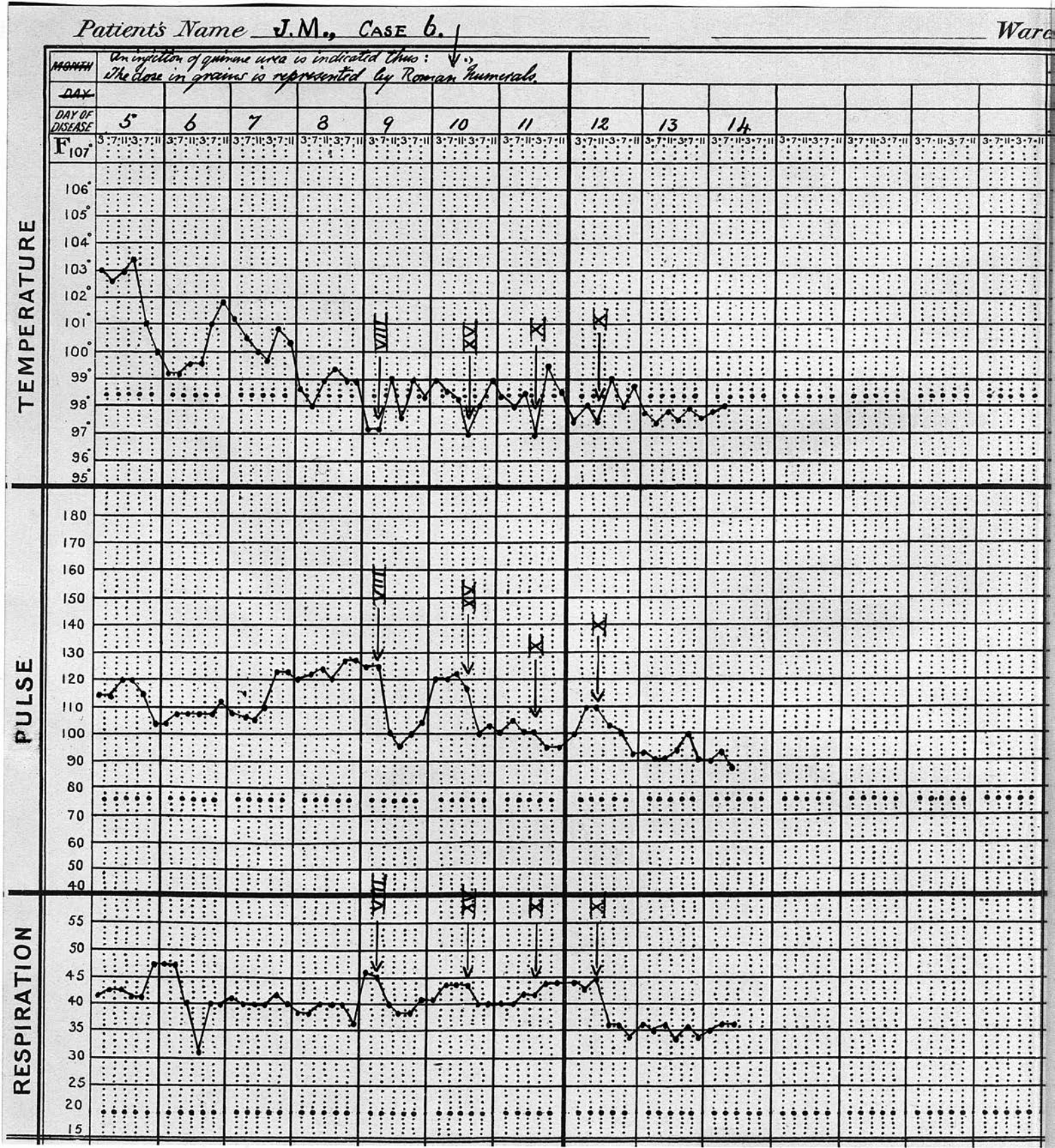
F 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96° 95°

PULSE

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

RESPIRATION

55 50 45 40 35 30 25 20 15



breathing was dyspnoeic, the cough hard and painful and the sputum streaked with blood. The temperature rose to 102° with irregular remissions. I administered ten grains of quinine-urea, but the oscillating nature of the fever prevented a determination of its effect on the temperature, and there was no apparent improvement in the general condition. The patient gradually sank, became very difficult to feed and passed by slow degrees into the typhoid state. She died on the seventeenth day of the illness. A post mortem examination was not made, but I am of opinion that during the last stage of the illness the pathological condition in the lung was largely a hypostatic pneumonia, while the broncho-pneumonia was in reality a secondary condition throughout. In all I administered four injections of quinine urea, one of ten grains, two of fifteen grains and one of twenty grains, when I discontinued the treatment as it had no apparent effect on the course of the disease.

CASE 6.

J.M., a woman, aged 62. This case was one of Dr. Syer White's patients, and I am indebted to him for permission to record it here. I was asked to see the case on the ninth day of the illness. The case was described as one of left-sided basal pneumonia which had run the usual course up to the fifth day of the disease, when there occurred what appeared to be a pseudo-crisis:

the temperature dropped without a corresponding fall in the pulse and respiration rate. The two succeeding days were characterised by an increasing pulse and respiration rate and a falling temperature. The following day, the eighth of the disease, the patient collapsed; the temperature fell to 97.8°, the pulse became extremely rapid and there was marked cyanosis. The condition continued critical. On the morning of the ninth day the temperature was 97.2°, the pulse 125 and the respirations 48. There had been incontinence of urine during the night, she was apathetic and there was profound muscular prostration. The left lower lobe was consolidated and there were signs of commencing consolidation on the right side. In view of the subnormal temperature it was not clear what effect an injection of quinine urea might have, but as her condition could not well be more critical we administered eight grains intramuscularly. The temperature rose within half an hour almost two degrees - from 97.2° to 99° - while the pulse rate fell to 100 and the respirations to 40. The improvement was not maintained, and the following day, at 6 p.m. the temperature had fallen to 97°, when a second injection of fifteen grains of quinine urea was succeeded by a more gradual rise in temperature and an improvement in the general condition which held throughout the night and well into the next day. During the afternoon unfavourable symptoms were again manifest and she received a third injection. In all four injections of quinine urea were administered,

Patient's Name R.G., CASE 7. Ward

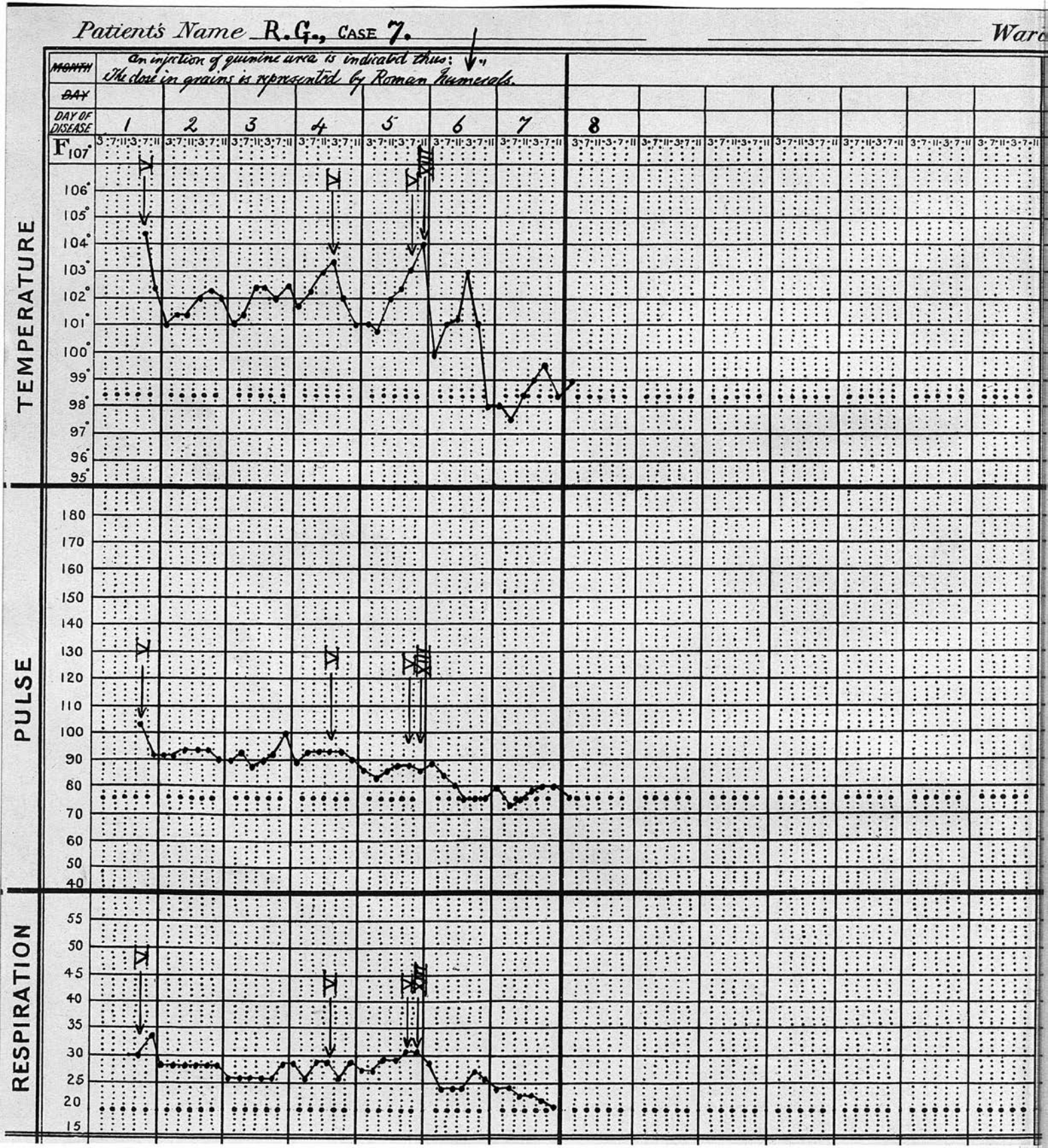
An injection of quinine urea is indicated thus: ↓
The dose in grains is represented by Roman numerals.

MONTH
DAY
DAY OF DISEASE 1 2 3 4 5 6 7 8

TEMPERATURE
F 107° 106° 105° 104° 103° 102° 101° 100° 99° 98° 97° 96° 95°
3·7·11·3·7·11

PULSE
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

RESPIRATION
55 50 45 40 35 30 25 20 15



followed in each case by a rise in temperature of a degree or more and a corresponding improvement in the pulse and respiration rate. The outstanding clinical feature of the illness was the marked asthenia. It seemed as if the pathological process in the lungs remained stationary, while the patient gradually sank under the weight of accumulating toxins which she was unable to react to except under the influence of quinine urea. Convalescence was prolonged.

CASE 7.

R.G., a boy, aged 19, was admitted to hospital suffering from a severe pneumonia of the influensal type. He was a groom and had been at work that morning. The rapidity with which toxic symptoms had appeared and his apparent collapse were evidence of the virulence of the infection. His temperature was 104.2° , his pulse 104 and his respirations 34. Fine indux crepitus was audible at both bases. There was cyanosis, dyspnoea and dilitation of the right heart associated with mitral incompetence - that the incompetence was due to disease of the valve and not to relative insufficienty was indicated at a subsequent examination. I administered intramuscularly one c.c. of camphor in oil followed by five grains of quinine urea. The temperature fell to 101°, the pulse rate came down to 92, and the symptoms of cardiac distress were relieved. During the second and third days of the illness there was a progressive weakening of the patient and an increasing

toxaemia associated with cardiac distress On the fourth day a severe epistaxis relieved the heart and a second injection of five grains of quinine urea was followed by a fall in temperature without any appreciable improvement in the patients condition. He now became rapidly worse. On the fifth day the temperature rose steadily, unchecked by a third dose of five grains of quinine urea, and when three hours later it had risen to 104° I administered a fourth injection of thirteen grains.of the drug. The temperature fell to 100° and coincident with the marked slowing and steadying of the heart's action there was a most gratifying improvement in the patients general condition. The termination was by lysis on the seventh day.

DISCUSSION.

The cases described illustrate in a more or less marked degree the salient features of quinine therapy. The coincident fall in temperature and relief of toxic symptoms, exphasized by Solis Cohen, is clearly demonstrated; while the improvement in pulse and respiration rate, though evident is generally less well marked. It will be observed that I have not employed the massive dosage, on which Solis Cohen lays so much stress; my reason for this is twofold, I wished to study the effect

of smaller doses and to control the case with the minimal effective dose. In one case only were the smaller doses inadequate; in this case, no 7, the first three injections of five grains each were obviously too small and it was not until a larger dose was employed that the desired effect was obtained. Case No.6 is very interesting. It illustrates the absence of any element of shock following the injections and suggests that the action of quinine urea in pneumonia is not necessarily followed by a fall in temperature but rather by a tendency to maintain the temperature at a level most suitable to the immediate needs of the organism. Case No. 5. illustrates the limit of usefulness of this drug; there was no improvement following the injections; primarily it was not a case of toxaemia but one of exhausted vitality, with a gradually weakening heart and hypostatic pneumonia.

A consideration of these cases and of the observations of Kolmer, Solis Cohen and others leaves little room for doubt that the administration of quinine derivatives to a pneumonia patient does profoundly modify the course of the disease. The nature of the action is obscure. Investigations for its elucidation have proceeded along two independent lines. On the one side the interesting possibilities opened up by Morgenroth's discovery - that ethylhydrocuprein hydrochloride renders the blood of mice pneumococcicidal and protects them against a lethal dose of pneumococcus - led inevitably to its clinical exhibition in pneumonia;

while on the other side Solis Cohen's experience of the clinical value of quinine urea in pneumonia led to experimental investigation of its action. The field of Solis Cohen's investigations broadened and came to include much ground that had already been covered by those experimenting with ethylhydrocuprein hydrochloride alone. Sir Almroth Wright, Moore, Chesney and others all experienced disappointing results when they came to administer ethylhydrocuprein hydrochloride to pneumonia patients. Sir Almroth Wright considered that the failure might be explained as a result of depression of the phagocytic activity of the leucocytes, or because the drug failed to penetrate the diseased lung in sufficient quantity. Moore and Chesney attributed the failure of the drug to the fact that it was too toxic to be given in quantity large enough to exert any considerable bactericidal action in the alveolar exudate. These views, while offering an explanation of the failure of ethylhydrocuprein hydrochloride in pneumonia, would suggest, on the analogy of Morgenroth's experiments and possibly also on that of the generally accepted action of quinine on the malarial parasite, that any benefit which might derive from the drug should be assigned to its bactericidal power. But a clinical investigation into the action of other quinine derivatives - especially quinine urea - had given results which could hardly be ascribed to bactericidal action. If the action were a bactericidal one relief of toxic symptoms would follow

destruction of pneumococci in the consolidated lung area, which, if it were possible, would no doubt be a slow process not in accord with the rapid improvement so frequently experienced. But indeed the failure of ethylhydrocuprein hydrochloride, the most powerful as a pneumococcicide, together with the fact that an adequate dose of quinine urea is far too small to have any pneumococcicidal power efectually disposes of the bactericidal theory.

The clinical experience and preliminary laboratory investigations reported by Solis Cohen and Kolmer appeared to indicate a neutralizing action by the quinine salt on the pneumonia poison-complex. Experiments undertaken in the hope of demonstrating such action were inconclusive and led them to suggest that the value of quinine in pneumonia might lie in its influence on general metabolism and on antibody production. A review of these experiments, refered to on page 12 and following pages, suggests that, as they are so largely negative and in some respects contradictory, they present no weight of evidence against the assumption that the value of quinine urea in pneumonia is of an antitoxic nature. There is,for example, no evidence that the soluble endotoxin with which the experiments were conducted and which was first described by Cole (19) is the poison responsible for toxic tymptoms in a pneumonia patient. In this connection it is interesting to note that the serum of a pneumonia patient is not more toxic to an animal than the serum of a normal man. But to

produce the symptoms associated with a pneumonia there must be present in the blood of the patient a toxin: pending the determination of this toxin, and the investigation of the action of quinine urea on it under conditions in all respects similar to those which obtain in the body it is not possible to draw positive conclusions from negative observations. That quinine hydrobromide has power to neutralize the poisonous property of pneumonic lung exudate is a fact of more potential significance than the negative results of all the other experiments. But here again its significance is limited by want of evidence as to whether its action is primarily on the toxin or the tissues; while, as in the case of the endotoxin, there is no evidence that the toxic lung extract, which Solis Cohen prepared with great care to avoid bacterial contamination, is responsible for any of the symptoms in a pneumonia. The toxic property of pneumonic lung exudate is removed by filtering through a Berkfeld filter. Dr. Gordon* ground up lungs showing grey hepatisation and filtered the exudate through a Berkfeld filter to remove bacteria, and he found that the filtrate possessed no toxic action when injected into rabbits.

An initial difficulty is presented to the consideration of the subject by absence of information as to the cause of death in many cases of pneumonia. Excluding secondary causes of death, such as endocarditis or otitis-media, the clinical picture may be one of such

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*Personally communicated: Dr. Gordon has kindly consented to my quoting his observation.

profound toxaemia as to be incompatible with life, or the patient may die with all the symptoms of shock, or again there may be no apparent reason for the sudden death of a robust patient with one lobe only conslidated. In the latter type of case, in an extended series of postmortem examinations for the purpose of making blood cultures Dr. Gordon* has informed me that he has almost invariably found that the blood in the right auricle was clotted and slightly adherent to the wall. The clot was unorganized, but that is not evidence that it was a postmortem clot. It may well be that its sudden formation in the heart was the cause of death, when there would not be time for it to become organized. If this inference, deduced from Dr. Gordon's observations, is allowed as a possibility it will become apparent that quinine urea might prove a valuable safeguard in this type of case apart altogether from its more general action. It is a common observation that it is often difficult to obtain blood for the purpose of examination from a pneumonia patient when that patient is in extremis. Gulland and Goodall (20) have explained this by demonstrating the greatly increased coagulability of the blood in pneumonia. This increased coagulability of the blood lends significance to the inference drawn from Dr. Gordon's postmortem observations.

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* Personally communicated: Dr. Gordon kindly consents to my recording this observation.

Cannon (21), Dale (22) and others have shown that where a patient is suffering from shock, from whatever cause produced, there is a constant indication of the degree of shock in the hemoglobin content of the capillary circulation. In cases of pneumonia approaching a fatal termination the hemoglobin content of the capillary circulation increase steadily and may reach 112% or more. These two factors alone - the increased coagulability of the blood and the alteration of the hemoglobin content - indicate a profound modification of the blood composition which must directly or indirectly effect an alteration in the blood functions; and it is open to investigation whether quinine, which is capable of limiting acid formation in the blood, can also modify these factors in any way. If its administration results in a restoration of a more normal condition of the blood there should be diminished risk of the possibility of sudden death from a blood clot in the heart; while evidence that quinine urea, when administered to a pneumonia patient, does alter the blood composition in the manner suggested would provide at least a partial explanation of its value as a therapeutic agent.

The protective response in the case of lobar pneumonia is characterised not only by the formation of protective substances (Doches (23).) in the blood serum, but by the deposition of fibrin in large quantity. What purpose the fibrin serves is not

clear but it may represent an effort on the part of the organism to localize as far as possible the invading bacteria. That the barrier which it forms is an insufficient obstacle is shown by the frequency with which the pneumococcus can be isolated from the blood; and its formation in such quantity provides yet another example of the extravagance with which nature's protective responses are characterised. The deposed fibrin is a foreign protein and as such provides a possible source of a poisonous principle which Vaughan (24) has demonstrated in all protein material and which is liberated when the protein material is split up. It is possible that the toxic symptoms in a pneumonia are to some extent in the nature of an anaphylactic reaction to such poisonous principle and that quinine urea may limit the formation of this toxin.

In septicemia peptone, when given intravenously is followed by rigors and certain characteristic changes in the blood. The immediate effect of peptone is to cause the leucocytes to disappear from the blood, and they presumably collect in the lungs. It is just like a sudden and unexpected advance of the enemy and the leucocyte army retreats before the advancing enemy - the toxic peptone - for strategic reasons. Having collected their forces at the base, and when fully armed, the leucocytes proceed out to meet the enemy and overwhelm them. Does quinine urea exert a similar

action in pneumonia; especially as we know that the action of peptone is non-specific?

Yet another field for investigation is suggested by the observations of Dr. Gordon (25) and others on the meningococcus which resembles the pneumococcus in some respects. They found that the correct antiendotoxin is only produced in horse serum when certain definite conditions obtain. It is not sufficient to inoculate the horse with a graduated series of tolerated doses of meningococci, as in the preparation of diphtheria antitoxin, such a course results in the production of a serum containing no antiendotoxin. A serum containing the correct anti-endotoxin is prepared with difficulty and only when the immunizing injections are minute and even then the presence of the antiendotoxin in the horse serum is a fleeting phenomenon indicating the delicate nature of the protective mechanism and its extreme liability to derangement. The influence of antimeningococcal serum, containing the correct antiendotoxin, on the mortality in meningococcal meningitis has been clearly demonstrated. It is possible that the body is capable of making antiendotoxin for the pneumococcus under favourable conditions and that in this action it may be assisted by quinine urea.

There are other problems of interest, such as the action of quinine urea on the hemolytic activity of the urine of pneumonia patients, elucidation of which might help to determine the mode of action of this drug.

It has been suggested by Lord (26) that the crisis and resolution of the pneumonic process is dependent on a local biochemical change in the course of which the acid death point of the pneumococcus is reached. In the absence of definite information as to the nature of the toxaemia the problem seems well nigh insoluble; where the factor concerned may be a soluble toxin absorbed from living or lysed pneumococci in the consolidated area, or a toxin liberated from deposited fibrin, or a combination of these two or where the factor may be represented as a ~~as a~~ faulty or incomplete response on the part of the tissues, the problem is not likely to be approached from the experimental stand point with much prospect of success. While from the clinical point of view much remains to be done. It is interesting to note that in attempting to explore a way out through the entanglements that beset this problem we come back to the shrewed observations made by Schultz nearly fifty years ago and based on clinical experience. It must be remembered that, so far as we know, the body is the only laboratory capable of producing nontoxic antibodies; and it would seem most reasonable to look for an explanation of the value of quinine urea in pneumonia to its power to so modify the conditions under which the tissues elaborate their antibodies that nature is able to produce and apply them to the best advantage.

SUMMARY AND CONCLUSIONS.

The above discussion clearly demonstrates that in quinine urea we have a most valuable drug for the treatment of pneumonia. It is applicable to all clinical types of infective pneumonias and should be regarded as an adjunct in treatment. The use of serum, especially Type I serum in Type I cases, is of course a well recognised form of treatment. The use of quinine urea is of far wider application since it can be used in any type of pneumonia, and does not suffer from the disadvantages connected with serum treatment, e.g. anaphylaxis, serum sickness, &c. It can be given either in the form of massive doses or in the form of small repeated doses. The interesting fact that patients suffering from pneumonia do not experience any ill effects from the quinine deserves emphasis here. It has been shown that such patients tolerate quinine very well even in large doses and this is true even of persons known to be intolerant to quinine at other times. The drug may be given by mouth, intravenously, or intramuscularly but not by subcutaneous injection. Where it is necessary to obtain rapid results or where small doses are desired the intravenous mode of administration is advocated. The intramuscular method is just as efficacious in most cases and is the method which I have latterly adopted.

Judging by the records of the cases described

in this paper this drug exerts a definite action on the temperature, and in many respects resembles the effect of Type I serum on Type I pneumococcal infections of the lungs. The improvement in the general condition of the patient is however so marked a feature as to warrant an extended use of the drug if only for this effect alone. This immediate effect of the drug is one which requires further explanation since there is no doubt that by pursuing this line of investigation a possible explanation of the exact mode of action may be forthcoming. That the drug does not exert a direct lethal action on the pneumococcus seems to be proven by the work of Solis Cohen, and also by the fact that the doses used in treatment are far too small to have any bactericidal action. The alternative mode of action of this drug would appear to be one of direct action on the tissues of the body in general. In this respect quinine urea may produce its action in a variety of ways. It may stimulate the formation by the body cells of anti-endotoxin, and such an action would be followed by an immediate improvement as occurs in meningococcal infection. (Vide Gordon.)

Quinine urea may exert a direct action on the coagulability of the blood, or upon the formation of fibrin or neutralize soluble toxins circulating in the blood. Again we may have a series of changes produced similar to those found after intravenous protein therapy with the production of protein shock. If as seems likely

the intoduction of peptone intravenously causes a rapid migration of nearly all the leucocytes into the lungs, may not quinine urea do the same?

The above are merely tentative suggestions, and simply serve to emphasize the fact that we know very little as to the mode of action of this drug, although the results of treatment are of such a satisfactory nature that an extended application of this drug seems amply justified.

The object of future work on this subject is to apply the drug to a large number of cases, and at the same time attempt to determine its pharmacological action. The investigation may be so arranged that data as regards blood changes, isolation and identification of endotoxin will be collectsd. The present paper represents an attempt to place on record my own experience with the use of this drug, to summarise the present state of our knowledge, and to make suggestions as to the lines of attack of this interesting and fruitful problem.

CONCLUSIONS.

1. That quinine urea is a valuable drug in the treatment of lobar and lobular pneumonia.
2. It acts by reducing the temperature and its use is followed by an immediate improvement in

the general condition of the patient.

3. The exact nature of the action of quinine urea in pneumonia is not understood. All evidence is against it exerting a direct bactericidal action on the pneumococcus.

4. The possibility of a direct action of this drug on the tissues of the body appears probable, and would explain many of the clinical features observed.

5. The application of this drug to a large number of cases of pneumonia is contemplated and the application of clinical pathological methods to these cases to determine if possible the true pharmacological action of this drug, and other quinine derivatives.

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