SCHIZOPHRENIA AND ITS TREATMENT by INSULIN and CARDIAZOL.

T H E S I S for M.D. Examination

— submitted by —

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October, 1939.

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C O N T E N T S.

I. INTRODUCTION.

Mental disease in its various forms has been recognised and written about for many years. It was mentioned in the Bible, Saul being a famous example. In Greece, there were many schools of thought regarding mental disease; many and varied forms of treatment were tried; flogging, chains and starvation were all used, venesection was also popular. Caelius Aurelianus was especially worthy of praise, for he placed his patients under the best conditions of light, temperature and quiet and recommended that everything of an exciting nature should be excluded; he emphasised the importance of tact in attendants and nurses. Entertainments, light sports and work were all recommended during the convalescent stage. Mediaeval Europe left the treatment of the insane to priests. In 1320, lunacy legislation appeared in England and gradually steps were made until at the end of the 18th century, the modern era of care and treatment of the insane began.

Mental disease is extremely important; up to a short time ago, people regarded mental illness as a great disgrace and even nowadays many people still think in that manner. If

a/

a member of a family developed a mental illness, the stigma was placed on all other members of that family. Mental illness is also very important in its relation to crime; another point is that mental illness immobilises a large number of people in every country of the world; by that I mean that mental hospitals the world over are full and in many cases overcrowded and to a great extent by people suffering from chronic mental illness. One of the chief causes of chronic mental illness is Schizophrenia.

Schizophrenia has struck at all classes of people, rich and poor, intelligent and dull, male and female. It often appeared when a young person was at the onset of a career, when the hopes of relations were high. Ellery(1) stated that schizophrenia claimed more victims than either cancer or tuberculosis and that in the U.S.A. each year some thirty to forty thousand young people would succumb to schizophrenia, for at least one quarter of the patients admitted to mental hospitals were suffering from this disorder. According to Henderson and Gillespie(2), fifteen to sixteen per cent. of admissions to mental hospitals were cases of schizophrenia and fifty to sixty per cent. of our permanent mental hospital population suffered in this way. At the hospital at which the

author/

author works; over the past six years, 2,983 patients have been admitted, of these 639 were cases of schizophrenia, this was about 20%. At the time of writing, there were 3,300 patients in the hospital, of these 990 were schizophrenics, this was about 30%. The cost of each patient per week was 25/8 so this worked out at about £1,237 per week or £64,324 per year for the cases of schizophrenia. As these people entered the hospital young, they tended to live a long time requiring long continual nursing care.

Many types of treatment of this illness have been tried but none has really succeeded. Each had their supporters and each had its day. Complete elimination of sepsis was tried, treatment with thyroid extract, various other endocrine drugs, prolonged narcosis with somnifaine, shock treatment ranging from sudden immersion in icy cold water to the production of rigors with T.A.B. vaccine. Each line of treatment claimed a certain amount of success, but none could be called a great success.

In view of the toll which schizophrenia claimed from humanity any form of treatment deserved a trial.

The originator of the insulin shock treatment of schizophrenia was Dr. Manfred Sakel,[3] he stated that he had treated some morphia addicts with insulin and thought that

insulin/

insulin abolished the phenomena of irritation during abstinence from morphia because the nerve cells were blocked and their function quantitatively affected. Starting from this point he attempted to influence other states of excitation by means of insulin. He[4] stated that insulin has been used often before by many other workers in the treatment of psychosis. There was, however, a fundamental difference in the use of insulin hypoglycaemia or hypoglycaemic shock, and the therapeutic intentions of all my predecessors. It was precisely those factors which they had previously tried to avoid because they were thought to be dangerous, which I at that time deliberately used as the effective and principal factors of my method of treatment. I should like to make it clear at this point that "insulin hypoglycaemia" is the term used here to describe the borderline insulin treatment as used for morphinism, with severe shocks, such as epileptic convulsions, avoided by the addition of barbiturates. The "hypoglycaemic shock treatment", however, consists of the deliberate production of severe shocks by the omission of barbiturates, and by the extension of the duration of the hypoglycaemia.

About the same time as Sakel was working at his insulin treatment; Von Meduna began to treat schizophrenia with cardiazol. He[5] stated that between schizophrenia and

epilepsy/

epilepsy there existed a sort of biological antagonism which must be expressed in the pathological course of the two diseases. Without being able to characterize these pathological actions, he felt justified in asserting a priori that these courses were either mutually exclusive or they did at least to a great extent weaken each other in their mutual effects. In 1929, Professor Nyiro published the results of his study of the material in the Budapest hospital. He found 1.5% spontaneous recoveries among 176 epileptic patients. But if the epilepsy was associated with schizophrenia, 16% recovered. This sixteen-fold difference in the homogeneous material of the institution was so great that Nyiro could not help noticing it and postulated an antagonism between the diseases. Von Meduna came to the conclusion that the artificial production of convulsions might help to cure cases of schizophrenia and the substance he chose to use was cardiazol.

Since these two lines of treatment started, other medical men have been trying out the treatments in all parts of the world.

The author's work has been done at the County Mental Hospital, Whittingham, Lancashire; the treatments have been on trial here for about 18 months. Male patients were treated

first. The author began treating female patients in January of this year 1939. My chief interest in the subject lay in the possibility that this treatment might help a number of young people who otherwise might become chronic primary dements to regain their former station in life, to be able to enjoy the former comforts of life and to be able to adapt themselves to life's difficulties; others who might not recover fully might become well enough to enjoy social contacts while still remaining in the mental hospital. I was placed in sole charge of the female patients undergoing treatment with insulin and cardiazol and although my numbers were small I have had an opportunity of learning the technique of the treatment. Permission was obtained from patients' relatives to start the treatment and both insulin and cardiazol were used, insulin more so, sometimes singly and sometimes together.

II. CLINICAL TYPES.

Schizophrenia, in its typical form, consists in a slow, steady deterioration of the entire personality, usually showing itself at the period of adolescence. It involves principally the affective life, and expresses itself in disorder of feeling, of conduct, and of thought, and in an increasing withdrawal of interest from the environment.

E T I O L O G Y.

The causes of the condition are obscure, there are many possible factors.

A G E.

Mapother[6]

Mapother[6] stated that in three quarters of the cases that ultimately exhibited the characteristic chronic syndrome, the onset of well defined mental symptoms dated from the period between 15 yrs. and 25 yrs. Cases occurred in quite young children, he saw a case in a child of 6 yrs. On the other hand many cases especially of the paranoid variety started after 25 yrs. and might do so as late as 40 yrs. Christian[7] stated that out of 4,163 schizophrenic patients admitted between 1929-1931 to all the mental hospitals of the New York State, 2,700 or 37% were between the ages of 15-34 yrs. Henderson and

Gillespie/

Gillespie[2] stated the great majority of cases started about puberty and adolescence and estimated that two thirds commenced between 15 and 30 yrs.

H E R E D I T Y.

When one interviewed relatives of Schizophrenic patients, one soon came to realise that not a few of these relatives were "odd" and "peculiar", and the question arose as to what role, if any, heredity played in Schizophrenia. Henderson and Gillespie[2] stated that heredity played an important role in Schizophrenia and quoted that 50-60% of cases had a family record of mental illness. The condition was not so frequently seen in parents and children as in brothers and sisters. Kraepelin[8] found hereditary abnormalities in 53.8% of 1,054 cases and a directly inherited taint in 33.7%. Rudin[9] found in a series of 721 cases, 40 siblings with schizophrenia and 79 with other psychoses. He also found that every fourth or fifth parent of schizophrenic patients had a mental or nervous disorder of some kind. In a study of 171 schizophrenic patients discharged from the New York State Psychiatric Institute, Horwitz and Kleiman[10] found psychoses or psychoneuroses in the relatives of 35% of the patients.

One might conclude that there was no distinct law or rule/

rule of inheritance in the occurrence of schizophrenia. From the practical standpoint with reference to advice regarding marriage, it appeared that one could not say that the children of two parents who had Schizophrenia would necessarily have the same disorder, although the chances of their having such a disorder were greater than if both parents were well adjusted normal individuals.

SEX AND RACE.

The sexes were fairly equally affected, no race seemed to be exempt from similar degenerations, though exact details of the clinical picture were considerably modified by the degree of culture.

PHYSIOLOGICAL STRESSES.

Kraepelin [8] believed that the disease resulted from an auto-intoxication following a disorder of metabolism and that this auto-intoxication was produced by a disordered secretion of the sex glands. In support of this view he urged the frequency with which the first symptoms showed themselves in relation to puberty. Mott[11] attributed the disease to a disordered action of the whole endocrine system. Mapother[6] reported several cases coming on during pregnancy and/

and after childbirth and thought that toxaemia and infection might play a part; these cases often shewed some confusion resembling those cases of Confusional Insanity definitely due to toxic factors.

RECENT MENTAL STRESS.

Mapother[6] stated that sudden shocks might occasionally appear to be the starting point of Schizophrenia but more often the stress was prolonged.

RELATION to REMOTE EXPERIENCE.

Meyer[12] attributed schizophrenia to the progressive maladaptation of the individual to his environment. Jung[13] stressed as the fundamental characteristic of Schizophrenia an habitual tendency to Introversion. The origin of introvert disposition was ascribed to early unpleasant experiences. By Freud,[14] the tendency to introversion was regarded as due to regression towards auto-erotism. He traced the origin of this condition to an accentuation and fixation in infancy of narcissism or some earlier phase of sexuality - due, at least, in part to experience of this period.

Any attempt in the direction of the early recognition of schizophrenia must begin with schizophrenic potentialities, therefore/

therefore the childhood of those individuals who became chronic schizophrenics must be studied. In the histories of most of these people, such adjectives as "quiet", "shy", "reserved", "cold", "indifferent", "unsociable" and "seclusive" often recurred; it would be fair to say that they did not meet the realities of their environment satisfactorily and that this maladaptation was manifested quite early in childhood. The brunt of the personality deviation fell not on the intellectual but on the emotional make-up, more often than not these children were intellectually bright, but they often became bored with the ordinary subjects of the curriculum and became interested in such subjects as Astronomy, Philosophy and Astrology. Perhaps the keynote of the child's personality was a shrinking from reality. These children were non-competitive; they longed for the prizes of competition but they disliked the endeavour that was required. Any growing tendency to reject contacts with other children and a preference for adult companionship or, failing this, an increasing drift in the direction of aloofness, reticence and isolation should be regarded with suspicion. Excessive daydreaming was common, daydreaming was normal in every child, but when it occupied a very large segment of the child's daily life and when the transition back from day-dreaming was somewhat difficult for the child, then daydreaming

was/

was attaining dangerous proportions Kraepelin[8] has described four types of character make-up as predisposing to schizophrenia.

(1) The quiet, shy, retiring disposition, making no friends and living only for himself.

(2) The irritable, sensitive, excitable, nervous selfwilled type with a tendency to bigotry.

(3) A smaller group who from childhood up were restless, lazy, disliked work, were inclined to nasty tricks, did not persevere at anything and became vagrants and criminals.

(4) In contrast to these were children, who were conspicuous for their docility, good nature, anxiety to please, conscientiousness and diligence, and as patterns of goodness held themselves aloof from all childish naughtiness.

Kunkel[16] named these types the Autistic, the Unstable, the Asocial and the Pedantic respectively.

In sharp contrast to these latent periods, schizophrenia occasionally developed with great suddenness. After some emotional shock, the patient might become immediately greatly confused or catatonic.

The quiet, shy, sensitive daydreaming child often developed an adult type of personality which since it was the antithesis/

antithesis of the social, energetic type or extrovert, was called Introvert. By Introversion was meant the turning in of the mind or self on to its own problems. The Introvert got his chief pleasure from within himself, the extrovert, from without. The introverts were the dreamers and inventors. The person who was introverted to a dangerous degree did not find the world a pleasant place in which to live; undoubtedly there was always in his mental life the conflict between the desire to grasp the fruits of endeavour in every phase of life and the shrinking from the effort that must be made before victory was secured. A decision had to be made; if his ultimate fate was to become a schizophrenic, he lost some small part of his hold on reality day by day and finally came the time when the verdict of failure was inescapable.

Regarding the physical make-up of these people Raphael[16] reported a rather definite type trend of soma obtains differing in its nature strikingly from that occurring in Manic-Depressive material. The body organization on the whole tended towards the linear cast of habitus with a relatively small narrow face and head and a long, shallow and less capacious type of trunk; the fingers were long and tapering, the costal angle was acute, the chest was long and narrow, and the extremities tended to be long. Lewis[17] reported cardiac and circulatory aplasia.

Gibbs[18] emphasised abnormal hair distribution, vertical pubic hair and hair on the face and elsewhere, being frequent in his female patients, and a horizontal distribution of hair, often with scanty hair in the beard region being common in males. Abnormalities in the texture of the hair, nails and in size and consistency of the testes were reported more commonly in schizophrenia than in any other mental disease. Kretschmer[19] stated that there was a clear biological affinity between the psychic disposition of the schizophrenic and the bodily disposition characteristics of the asthenics, athletics and certain dysplastics.

During the prodromal stage of schizophrenia, Jelliffe[20] called attention to fatigue, real or apparent, as an early sign; he believed that it was evidenced by flagging attention. Changes in mood were common, sudden rudeness, excessive sluggishness, irritability and quarrelsomeness often indicated more than the normal amount of mental fatigue. Masturbation was common and its resulting conflicts occupied a prominent place in the person's consciousness. Ideas of reference developed and there might be a display of Negativism. The earliest symptoms were often a withdrawal from reality, the pre-occupation with day-dreams, with the result that there was a progressive diminution of voluntary attention and long periods of abstraction.

Kraepelin [8] originally described four clinical types of schizophrenia and I have placed my cases into these four types, namely, Dementia Simplex, Catatonia, the Paranoid form and Hebephrenia.

Dementia Simplex was generally insidious in origin, the outstanding feature was introversion in which could be noted a generalised diminution of the response to external stimuli and particularly of affective responses to such. People suffering from this complaint appeared to lack ambition, they were content to lead idle lives, often they frequently changed their employment, they often became vagrants wandering from place to place with no goal in sight. Such people did good work but always in a subordinate capacity. As time passed, they became moody and irritable especially if efforts were made to stir them up. All thought became difficult, they were often incoherent. They had no insight into their condition and the chief feature was the extreme apathy.

CATATONIC TYPE.

In those persons who developed the catatonic form, the shut in personality was frequently not present, but the history shewed that they tended to be sullen, unsociable and suspicious.

The onset might be acute. It was usually described as an alternating state characterised by a depressed stage, an excited stage and a stuporose stage. There might be complaints of headache, difficulty in thinking, other pains and fatigue. Disconnexions in the realms of intellect, emotion and conduct all occurred. Spontaneous conversation did not quite hang together, replies to simple questions might be slightly irrelevant. Mapother[6] has referred to this as "The Knight's Move" type of association. Some patients uttered a regular protest against their detention, they accepted a refusal politely. Isolated emotional displays of various types were common; no apparent external reason for these could be ascertained; they were doubtless due to hallucinations and delusions.

The most distinctive symptoms illustrating the fragmentation of association which is termed schizophrenia were those disorders of conduct grouped under the terms "Catalepsy" and "Catatonia".

In Catalepsy, the impulse came from without, we got automatic obedience to orders. Flexibilitas Cerea, Echopraxis and Echolalia. In Catatonia, the impulse came from within and we got impulsive actions and utterances, Catatonic excitement,

spontaneous/

spontaneous fixed attitudes and expressions, Stereotypics of conduct and speech. Negativism also occurred in the Catatonic type, it manifested itself as Mutism, Resistiveness and Mischievousness.

PARANOID TYPE.

This type of reaction was apt to develop later in life than the other types in persons of better than average intelligence. However they were usually sensitive and disliked criticism. Aggressiveness might show itself as a compensation for lack of confidence. The onset of frank mental symptoms might be gradual with increasing suspiciousness and the development of persecutory feelings. Anditory hallucinations predominated, threats of bodily harm were heard. Trivial, ordinary incidents were misinterpreted as referring to the patient. The patients protested vigorously against their persecutors and showed at times a violent emotional reaction. The delusional trend however was not as systematic and elaborated as in the true parancia and the delusional ideas became at times bizarre and illogical. Some patients as time passed tended to lose their aggressive emotional reactions and accepted the illogical ideas without protest; along with this their conduct deteriorated. Others, however, developed a

compensatory/

compensatory, expansive type of reaction in which they became more and more powerful, developing a feeling of superiority. They often identified themselves with very important personages. They merely had these ideas and accepted them as true, in this respect they differed from the true paranoiac who worked out a logical, plausible elaboration of his ideas.

HEBEPHRENIA.

This type of reaction tended to come on at or soon after puberty. The outstanding symptoms might appear gradually with increasing withdrawal from reality but with added symptoms of ideas of reference and hallucinations of a fantastic nature. Features of both the Catatonic and Paranoid forms appeared. The emotional response was shallow, patients laughed and wept without any adequate cause, or had sudden violent outbursts of anger, explosive in character and rapidly passing away. Bleuler[21] described hebephrenia as the great trough into which were thrown the cases that could not be classed in the other three types.

It was generally recognised that schizophrenia was a serious disturbance. The prognosis was bad; this was only for the schizophrenia seen in mental hospitals which as Mapother[6] said was but a pernicious form of a very common variety of

maladjustment/

maladjustment that often ended favourably.

Remissions occurred in this disease, they might be of any length up to several years and occurred in all the types. In forecasting the future of an individual case only a few data were available. No idea was known what determined the recovery in a great many cases, but certain features in the history and certain details of the symptoms were noted that rendered it more likely.

(1) A history of previous attacks followed by a remission, indicated the possibility of the same thing happening again.

(2) The duration of the present attack was important. Continuance of symptoms over 12 months implied a poor chance of recovery. Before 6 months, very little could be said.

(3) The more rapid the onset and the more clearly related to traumatic experiences, the more hopeful the prognosis.

(4) The more the symptoms represented the gradual evolution of an abnormal personality, the worse the prognosis.

(5) The presence of hallucinations combined with a clear consciousness was a bad sign.

Signs of approaching dementia were increasing apathy, elaboration of delusions and the presence of stereotypics.

From the point of view of treatment with insulin and cardiazol, the following factors were important.

I. LENGTH of ILLNESS.

All authors were agreed that the shorter the illness, the better the chance of recovery. Frostig[22] stated that he treated 23 recent cases and 30 old cases by hypoglycaemic shock. Of the 23 recent cases, 20 showed a complete remission, 1 incomplete improvement, 1 negative result and 1 died. The % of complete remissions was 86.9%. Of the 30 old cases, 7 showed a complete remission, 3 incomplete improvement, 5 slight improvement and 15 no improvement. The % of complete remissions amongst old cases was 23.3%. Frostig went on to say that insulin treatment would abolish schizophrenic symptoms in practically every case of less than 18 months' duration. Berno[23] reported that in recent cases up to 6 months, he obtained 77.2% complete remissions, 18.8% improved, 4.5% relapsed. In 9 older cases, there was 14% complete remissions, 45.4% improved and 21.4% relapsed. Sheer[24] stated that acute cases had the best prognosis but the most uncertain diagnosis.

Von Meduna and Friedman[25] stated

(1) In the acute and subacute schizophrenic disorders (lasting less than 1 and 1½ years) remissions were obtained in/

in nearly 52% of cases.

(2) In chronic schizophrenia (lasting longer than 1½ years) there was a remission rate of 10%. This would have been markedly increased if the selection of cases had excluded very chronic disease, namely of more than 5 years, which made up much of this group. Much improvement was obtained in an additional 37%.

II. TYPE of SCHIZOPHRENIA.

Muller[26] found that the paranoid cases of schizophrenia showed the highest % of improvement, provided that they were not of more than 1 year's standing. Where the duration of the illness was over 1 year, cases of catatonic excitement did best. The Hebephrenic and simplex cases did the worst. He also stated that in making a preliminary survey of his material, he found that the number of cases which benefited from the insulin treatment was equal to the average remission rates that had been reported so far.

According to Reese[27] patients with early paranoid and agitated catatonic disease offered a more favourable prognosis with insulin, whereas stuporose catatonic and depressed hebephrenic subjects responded better to cardiazol. Advanced paranoid and delusional hebephrenic patients must be

treated/

treated according to their response. Kronfeld and Sternberg[28] found that in their female patients, 35% - 40% showed sufficient improvement to be discharged and in the males rather more than 50%. They further stated that the prognosis of hebephrenics was unfavourable, also all cases beginning very gradually and following a symptomless course. Hypochondriac paranoid forms were relatively unfavourable. The better the affective group the better the prognosis.

Sheer[24] reported that the paranoid type reacted better than the catatonic, this was of interest because in the paranoid type in contra distinction to the catatonic, the spontaneous remissions were rare.

Lehmaun-Facius[29] reported good results in paranoid types in contra-distinction to catatonic types, the latter reacted better to cardiazol.

Stalker, Millar and Jacobs[30] concluded that:

(1) There was no significant difference in the numerical results obtained in schizophrenia by ordinary hospital treatment, hypoglycaemic treatment and convulsant treatment. 218 cases were considered.

(2) Spontaneous remissions occurred most often in acute schizophrenic illnesses which could not be fitted into the standard subgroups, and in cases in which the affect was well preserved and there was little or no disharmony between mood and thought.

(3) Hypoglycaemia gave the best results in the paranoid group and in cases in which the affect was well preserved.

(4) Convulsion therapy appeared to be best suited for stupor reactions.

(5) The field of the special treatments was very limited but that each should be used in the special types of cases indicated. They afforded the best chance of recovery to a potentially recoverable patient whose illness was dragging on.

III. PLACE of TREATMENT.

The treatment was not just a mechanical treatment. It required a fair degree of skill; it could be compared with a major surgical operation and the results would vary according to the healing skill of the doctor and nurses in charge of the patient.

III. INSULIN TREATMENT.

The insulin treatment at the author's hospital was carried out in a special department. The department consisted of a dormitory of nine beds, one padded room, two single rooms, a dayroom, a clinic containing sterilizer, emergency kit, etc., and a M.O's office. The M.O.'s office led off the dormitory, so he was never far away during treatment. The department was in a quiet part of the hospital. During the morning extra mattresses were kept under each bed ready to be pulled out if a patient became very restless. Padded cushions were designed to fit over the headpiece of the bed.

The staff were picked, no-one had had any experience but all members were given all types of jobs to do. e.g. Nasal Feeding, so that if an emergency arose the routine work could be carried on without the M.O. or Charge Nurse.

Patients usually came from the Admission Ward to the Insulin Ward, occasionally there was a direct admission to the Insulin Ward, this meant that the patient underwent a complete physical examination by different M.O.s, a double check was thus kept on the physical state of the patient.

Whilst in the Insulin Ward and before treatment actually began, a blood sugar tolerance test was performed. The body weight was noted, and taken once per week during treatment.

There were certain contra-indications to Insulin treatment, these were :-

(1) Pulmonary Tuberculosis,
(2) Cardio-Vascular Disease,
(3) Kidney Disease,
(4) Liver Disease,
(5) Pancreatic Disease.

Treatment commenced at 7-30 a.m. every day of the week with the exception of Sunday, the patients having fasted from 7 p.m. the previous evening. The dose of Insulin was estimated on the previous day, after treatment had finished whilst the morning's incidents were fresh in the mind. Before giving the Insulin I always asked if each patient had eaten a good dinner and tea on the previous day. Special notice was also taken of late shock, vomiting and conditions of Pyrexia.

I started by giving 15 units of insulin intramuscularly, and increased the dose daily by 5-10 units until the initial coma dose was reached. This varied in my case from 20 to 135 units. From 7-30 a.m. onwards, pulse, temperature and respiration readings were taken every half hour until treatment was over for the morning; these were made on a card and any other observations such as myoclonic twitchings or commencement

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of coma were made on another card with the time.

It was customary to divide the treatment into three stages, the first in which the patient was given insulin in gradually increasing doses until a coma was produced; the second in which the dose of insulin was maintained at just the level to bring about a coma and the third stage when the insulin was gradually withdrawn.

The appearance of coma was heralded by numerous physical and mental changes. These symptoms differed in various patients, and at times changed from day to day in the same patient, although in my experience the patient usually reacted in the same manner. The first noticeable sign was drowsiness, some patients passed from this stage into coma very quietly, others manifested prodromal restlessness; varying from throwing the arms about and kicking the knees up, to throwing themselves out of bed and rolling about on the floor. Flushing was usually noticeable in this early stage. The pulse was generally accelerated but later brady cardia might appear. I liked the coma to be commencing between 10-15 a.m. and 10-45 a.m. I thought that the conjunctival reflex was more important than the corneal reflex for determining the onset of coma, for by the time the corneal reflex had gone the patient was in a deep coma. Liepmann[31] considered that the behaviour

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of the conjunctival reflex was useful as a guide to the depth of coma. As long as the conjunctival reflex was present coma was absent. Myoclonic twitchings of the whole body sometimes occurred in the early stage, at first I thought these might be the precursors of a fit and I terminated the Hypoglycoemia, later I found that I could safely leave these patients; for the myoclonus after lasting from five to thirty minutes passed off and the patient passed into coma. By the time coma was commencing, all my patients were perspiring, some more than others; also as an accompaniment to the onset of coma was an increase in salivation. At this point all the patients were rolled on their sides to allow the saliva to run out. The patients presented a miserable appearance, the skin had become pale, they were bathed in perspiration and from their mouths saliva was pouring. The tendon reflexes were absent or markedly diminished, an extensor plantar response appeared, the pulse was slowed. During this stage the patients had to be watched most carefully. I did not leave them in this state very long, 45 minutes being about the longest time left in deep coma.

Several patients of mine never went into a deep coma, instead, when other patients were commencing coma, they became very restless, rolling about the floor of the padded room;

salivation/

salivation and perspiration were profuse, the pupils were dilated and the pulse was very quick. This stage was allowed to continue for about 30 minutes.

To terminate the Hypoglycaemic state, 150 grms of 50% glucose was given; those patients able to drink took it with a little lemon juice. The others were fed through a nasal tube; the glucose was kept warm and diluted with a further 4 ozs. of water. I found that by doing this the patients came round quicker, presumably because a warm and diluted solution was absorbed quicker from the stomach.

Hunt and Feldman[32] found that some of their patients failed to rouse after an ordinary feed of glucose; they therefore supplemented the sugar solution with about 10 ozs. of warm water, there was an immediate and striking acceleration of reaction from shock in every patient.

Larkin[33] stated that he passed the nasal tube as soon as the patient was in coma and attached it to the cheek ready for use. I did not do that as I thought that it would increase the naso-pharyngeal secretion and increase the danger of aspiration.

The M.O. who had been watching the patients decided who to feed first, the nasal tube was passed by nurses, all got a

turn/

turn at this; at the same time another feed might be carried out. Gastric juice was drawn off and squirted into a bowl containing litmus paper, when it turned red the glucose solution was poured in. The time of the feed was noted on the patient's card.

The time taken to come round was regarded as very important, the patients varied again; I liked my patients to have commenced dressing themselves within 45 minutes of being fed. During this coming round stage the patients were often noisy and talkative. I frequently noticed that the first thing said was an incoherent recital of the alphabet, this gradually became more coherent.

During this stage Larkin[34] has developed a system of "Mothering the Patient", he stated that, each patient had one of the nurses or myself as "Mother Surrogate". Every effort was made to establish a rapport as the patient returned to consciousness. He was actually stroked and embraced. It was of the greatest use in the very apathetic type of patient. His first interest being in the person mothering him as he returned to full consciousness after interruption of the coma. During the first few days, as soon as full consciousness returned, the patient relapsed into apathy. Later he retained

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the warm feeling to his Mother Surrogate but dealt with it on a higher plane. He became self-critical and only manifested his affection to an extent that did not make a fool of him.

The author encouraged the staff here to try to mother the patients when they were coming round; but discovered that it was quite an art, one nurse could get on very well with one patient whilst another could make no impression on that patient. It was, however, in my opinion an important link in the whole chain of treatment. It was only at that time that some patients were accessible. At this stage I also attempted to influence some patients by continual suggestion, as it seemed that they were very prone to suggestion.

When the patients were round, they were given a piece of cake to eat, on the whole this was much enjoyed. Following this the patients were towelled down, then they dressed, made their own beds and then had their mid-day meal at 1 p.m.; which consisted of two courses, meat and vegetables, and a sweet rich in carbohydrate.

During the whole of the morning a fire was kept in the Insulin ward.

In the afternoon patients were encouraged to occupy themselves. In fine weather walks were arranged; the nurse

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in charge of these walks was always one from the Insulin ward, and she carried a supply of barley sugar sweets. The evening meal was at 6 p.m. and was rich in carbohydrates. No food was given after 7 p.m. After the meal games such as Cards, Dominoes, Draughts and Table Tennis were encouraged, and dancing to the wireless was popular. All patients were sent to bed at 9 p.m.

Treatment was continued until the patient was considered recovered. If there was no improvement 50 comas were aimed at.

At any time Cardiazol might be given instead.

Domaszewese[35] reported on 12 schizophrenics, who exhibited no change after treatment with 60 doses of insulin and were changed over to Cardiazol treatment with the result that 7 underwent a complete remission and improved. At the end of treatment insulin was again given. Whilst on the other hand, 17 cases who had been treated earlier with cardiazol alone exhibited only 4 complete remissions and when treated with insulin responded with a further 6 complete remissions.

Sakel[36] stated that three factors were absolutely necessary to obtain a lasting and satisfactory improvement by pharmacological shock treatment.

(1) the provocation of the proper type of shock for the particular case. i.e. either of a convulsive epileptic attack or of a comatose state. For the latter case it was particularly necessary to watch the appropriate depth of the coma.

(2) The termination of hypoglycoemia or shock at the most appropriate moment. This interruption time differed with the different clinical pictures of the psychoses.

(3) A correspondingly long treatment. The treatment should not only cease with the disappearance of the secondary psychotic symptoms, but it must be continued until those symptoms disappeared, which he called "activated psycotic" symptoms.

There were certain contra-indications to the treatment, these were :-

(1) Pulmonary Tuberculosis.

(2) Cardio-Vascular disease with a non-compensated heart.

I treated several cases with valvular disease of the heart following rheumatic fever.

(3) Kidney diseases.

(4) Liver diseases.

(5) Pancreatic diseases.

I made it my habit to have one individual talk per week, at least, with each patient undergoing treatment. No deep mental probing was attempted, but rather simple suggestion and encouragement were aimed at. At a certain point the question was put to them, "Do you realise why you are here ?" and if insight had not been regained then they were told so in a simple straightforward manner. After this I often found that the patient relapsed somewhat but the relapse was of an emotional type and soon cleared away. Cameron and Hoskins[37] stated that they did not apply any deep psychotherapy to their patients and they found that their psychotherapeutic endeavours were more successful if they were addressed to keeping the patient as tranquil as possible during the entire course of treatment.

Reese and Vander Veer[38] used a variation in the administration of insulin; after the findings for the blood and urine had been checked for several days, they gave 60 units of insulin intramuscularly at 7 a.m. on an empty stomach and from this point they moved up and down the scale to a satisfactory dosage figure.

There were certain possible complications of the insulin treatment.

(1) CARDIO-VASCULAR COLLAPSE.

Without doubt, insulin hypoglycoemia was a severe strain on the heart and circulation, producing as it did a sugar shortage for all the muscles of the body. Hadorn[39] stated that a shortening of the S-T. interval and an inversion of the T wave took place in the electrocardiagraph during hypoglycoemia, but these changes were reversible, and he concluded that a healthy heart soon recovered by the administration of glucose at the termination of the coma. In pre-existing cases of cardiac disease this reversion might not occur. James, Freudenberg and Cannon[40] reported a case of cardiac collapse. There was a history of previous cardiac collapse and the treatment was undertaken with reluctance. 28 comas were given without serious incident, except that irregularity of the pulse was frequent and was accompanied at times by cyanosis. The 29th coma was induced by 70 units, the same dose as on the preceding day. At 10-5 a.m. an epileptiform attack occurred, followed by an unusual pallor. The patient suddenly became pulseless and his veins were so collapsed that intravenous glucose proved impossible. 0.5 c.cs of adrenalin, 1 in 1,000, was given subcutaneously, followed at once by 2 c.cs of 33 1/3% glucose intracardially. Restoration was immediate and intra-venous glucose became possible.

There were no subsequent ill effects but treatment was given up.

The great disadvantage appeared to be the collapse of the veins, and intracardiac glucose appeared to be the right treatment if intra-venous injection was impossible. It should, of course, be followed by intra-venous or nasal glucose.

(2) LARYNGEAL SPASM.

I had two cases of this complication; one occurred 3 hours after injection of insulin; the patient had been in coma for 30 minutes. She developed sterterous breathing with marked inspiratory stridor and became cyanosed. Oxygen was given through a nasal catheter and the condition passed off only to return in 10 minutes time. This time the coma was terminated by glucose through the nasal tube. The spasm ceased in 3 minutes. Treatment was suspended on the next day but was continued two days later with a smaller dose. The patient eventually recovered and was discharged. The second case developed the complication 10 minutes after being fed, it was fairly typical; the patient had had a 70 minutes coma. 40 c.c's of 33 1/3% glucose were given intravenously and the condition cleared away quickly.

Finiefs[41] reported two cases of laryngeal spasm; the

first/

first, a female, approximately an hour after the onset of the third coma, developed very noisy respiration with inspiratory stridor lasting for a few minutes. She was becoming cyanosed when the stridor ceased and her breathing became satisfactory again. A few minutes later the same signs appeared again and coma was interrupted. The second, a male who had been in his 17th coma for 1½ hours developed inspiratory stridor with increased respirations and he became very cyanosed. 1 c.c. of adrenalin, 1 in 1,000, was given subcutaneously followed immediately by 6 mgms. of lobelline and 60 c.cs of glucose solution intravenously. He recovered almost at once. In both cases treatment was resumed with smaller doses after a rest of a few days.

(3) ACUTE OEDEMA of the LUNGS.

This was regarded as a rare complication, fortunately so. Strecker[42] stated that it was the most dangerous complication of insulin treatment. Finiefs[41] reported a case. He thought it might be due to some degree of pre-existing myocardial degeneration. A male patient began his 8th coma 2 hours 40 minutes after an injection of 75 units. He was left in coma for 1 hour 55 minutes during which time he had two tonic spasms alternating with hypotonus. He

perspired/

perspired freely and at no time did his pulse or respirations give rise to any concern. His coma was interrupted while in hypotonus. 20 minutes later whilst still unconscious, he had a fairly long and intense hypertonic spasm. He was very rigid and in opisthotonus. He was given 120 ccs. of glucose solution intravenously and the rigidity subsided but he was restless. Whilst preparations were being made to do a lumbar puncture, the patients respirations suddenly became hurried and shallow, and dyspnoea soon became severe. Cyanosis increased and he was very restless in his endeavour to breathe. He expectorated a large quantity of watery frothy fluid which was also streaming from his nose. His pulse was feeble and intermittent. Morphia grs. 1/4 and Atropine grs. 1/100 were given subcutaneously, Lobelline 9 mgms. and Coramine 5 ccs. intravenously followed by 10 ccs. of Euphyllin in 10 ccs. of glucose solution, also intravenously but very slowly.
Some amelioration in his breathing and pulse followed shortly afterwards, although there was still a good deal of dyspnoea and cyanosis. Moist sounds were present over his whole thorax. Continuous inhalation of oxygen was given but it was not tolerated at first owing to restlessness. He expectorated more frothy fluid and later vomited in an explosive way most of the glucose solution he had received through the nasal tube 2 hours previously.

A further 10 c.cs of Euphyllin in 10 c.cs of glucose solution was given intravenously. His breathing slowly but gradually improved and expectoration ceased. His temperature was 102.4°F, pulse 120, of poor volume but regular. His respiratory embarrassment lasted 3 hours, but he remained in a stuporous condition for 14 hours. After 9 days of pyrexia and bronchitis he recovered. Further insulin therapy was discontinued. Additional measures for this complication were venesection and very slow intravenous injection of 1/25 gr: of Stropanthin in 20 c.cs of glucose solution.

(4) PREMATURE INCIDENCE of COMA.

In some of my cases, coma commenced between 9 a.m. and 9-20 a.m. i.e. 1½ to 2 hours after the injection. These patients required very careful watching that morning; coma had appeared too soon, and it was found that it deepened very quickly. I always terminated these comas within 30 minutes, and the patient came round all right. On the next day the dose was reduced. This complication was thought to be due to an actual overdose or to an increasing sensitivity of the patient to insulin.

Petrie[43] regarded sensitivation as a most important phenomenon, he stated that usually after the dose had been

gradually/

gradually raised to that necessary to produce coma, it was sufficient to maintain that dose during the series of coma; at times the patient became unduly sensitive and a much lower dose had to be given. The early onset of deep coma might indicate this and it became necessary to cut down the dose until a new equilibrium was established. In a given case the dose was found to be 140 units and then too rapid coma developed, the dose was cut down to 100 units and later to 60 units. Muller[44] attributed this undue sensitivity to insulin to insufficient glycogen reserve in the liver and other organs and recommended that an attempt should always be made to diminish the amount of insulin once the coma dose had been reached. Finiefs[41] reported a case in which the patient became unconscious 1 hour 20 minutes after the injection of the usual dose. During the next 60 minutes he had two tonic spasms, the second being very intense, his pulse was imperceptible. He was given glucose nasally. 15 minutes later he had a fit, glucose was given intravenously but with no effect. He remained unconscious for a further 9 hours; he recovered however. Treatment was resumed after two weeks with a smaller dose.

(5) CONVULSIONS.

These occurred at any time during the hypoglycoemic state/

state; their etiology has not yet been satisfactorily explained. At first I looked upon them as being extremely serious; but later I found that a fit occurring early in the hypoglycoemic state i.e. in the first 1½ hours before the onset of coma was not so serious; the patient could be left for a further 30 minutes under careful observation of course, and then have the hypoglycoemia terminated with nasal glucose. If a fit occurred 3 - 4 hours after the injection, I regarded it as serious and took action immediately. Glucose through the nasal tube was given along with 1 cc of Adrenalin 1 in 1,000. If necessary, more glucose was given intravenously. In my series of cases I have had 19 fits early on and 8 in the later stages. Gillman and Parfitt[45] stated that they used a nasal glucose feed for pre-coma fits and extended this practise to fits in coma when they occurred early and the patient's condition was satisfactory. Dussick[46] stated that the delayed epileptic seizure was an absolute indication for the immediate administration of glucose. He gave 100 ccs. of 33 1/3% solution intravenously and followed it at once with sugar through the nasal tube. I found that if I gave 1 grain of Luminal at 8-30 a.m. to those patients who tended to have early fits then very often the expected fit did not occur.

(6) DELAYED RETURN TO CONSCIOUSNESS.

I liked all my patients to be dressing themselves within 45 minutes of having their glucose. If they were not doing this I regarded it as a delayed return to complete consciousness, and gave more glucose. One way was intravenously, 40 ccs of a 33 1/3% solution, another way was 4 ozs. of 50% glucose by mouth. In one case where the arm veins were poor and I was unable to give an intravenous injection I gave 1 cc of 1 in 1,000 Adrenalin.

In all cases the patients came round within 30 minutes, and especially quickly when an intravenous injection had been given. James, Freudenberg and Cannon[40] quoted a case of delayed return to consciousness. A male patient, aged 24 years, of excellent physique, had had 29 comas with no improvement. It was decided to extend the length of coma. The 30th coma was induced by 130 units. He became unconscious at 9 a.m.; at 10-45 a.m. the corneal and plantar reflexes had disappeared and the patient was hypotonic. He was left in this deep coma until 11-20 a.m., coma was interrupted in the usual way, but at 11-50 a.m. he was not awake, restless movements with opisthotonus and flushed face were noted. The corneal reflexes were present, but the plantar responses were

both/

both extensor. The pulse rate rose to 140 and the blood sugar was 230 mgms per 100 ccs at this time. This estimation was not known when 100 ccs of glucose were given intravenously in the belief that the above symptoms were due to hypoglycoemia. If Hypoglycoemia persisted after the tube feed, awakening after intravenous glucose was certain and immediate. The difficult cases were those in which coma persisted in spite of hyperglycoemia. This man slowly recovered.

It appeared to me that this dangerous complication could be avoided if the patient was not left in deep coma for a lengthy period, if a definite time for coming round was fixed (e.g. 30-45 minutes) and if great attention was paid to what had happened on the previous day. Dussick[46] made it a practical rule to intervene and give intravenous glucose at once if a patient did not awaken or show any definite signs of awakening within 30 minutes after giving the sugar.

(7) LATE SHOCKS.

By this was meant after effects; mild, such as somnolence and perspiration, or severe, such as rapid onset of coma/

coma or fits, coming on in the afternoon or evening. Most of my late shocks were of the mild type, and only on one occasion did a patient relapse into a coma. It was her 17th coma, she had had 60 units of insulin, coma commenced at 10-50 a.m., and was interrupted at 11-45 a.m. with glucose given nasally, she came round normally, was dressed by 12-45 p.m.; she refused her dinner and at 3 p.m. she collapsed in the ward, I found her in a comatose state. 50 cc's of 33 1/3% glucose solution was given at once intravenously, within 5 minutes she was awake, and able to drink a further 4 ozs. of glucose solution. All the others reacted to half a glass of 50% glucose solution by mouth.

All of my cases who developed late shocks had either a vomiting attack or refused their dinner. It seemed to me that there was some danger of patients becoming comatose during the night and being thought to be sleeping naturally. All patients undergoing insulin treatment slept under observation. Wilson[47] in her report of insulin therapy mentioned that the first fatality in Vienna occurred during the night. Gillman and Parfitt[46] stated that there were two factors in the production of late shocks; the first was the intake of food, the second, the prolonged action of insulin or the stimulus of

food/

food to insulin production. They believed that the latter alternative could be decided in favour of the prolonged action of insulin; for although after shocks sometimes occurred with a satisfactory food intake, they were commonest when the intake was insufficient. James, Freudenberg and Cannon[40] stated that their cases were due to insufficient food or vomiting and stressed the importance of training the nursing staff to recognise the symptoms.

8. V O M I T I N G.

In my series of cases I had 7 cases who vomited at different times after they had been fed with glucose. It seemed that there was a personal idiosincrasy. Gillman and Parfitt[45] found the same thing, and suggested that the nausea and vomiting was of a central origin. I came to believe that some cases of vomiting were directly due to swallowing saliva and nasal secretions, and these patients were continually kept on their side. When the gastric juice was being drawn off, great lumps of swallowed nasal secretion were brought up and I drew off the juice until it was free of this secretion; to the feed I added a tablespoon of simple bismuth mixture. This greatly reduced the incidence of vomiting.

Larkin[33] stated that if a patient had a tendency to

vomit/

vomit his glucose solution, the addition of an ordinary alkaline powder to the powder would prevent it.

R.S. Ellery[1] stated that to the unfamiliar observer, hypoglycoemic shock therapy might look particularly dangerous and somewhat cruel. One should not, however, judge by appearances alone. In the hands of a competent physician who had familiarised himself with all aspects of the treatment, the dangers were often more apparent than real, because so long as the doctor was in constant attendance, the patient could be brought to consciousness within a minute or two. It should go without saying that the psychiatrist who undertook this treatment would tread warily until he was personally familiar with it. He would, of course, be ever on the side of safety and tend to terminate the coma too early, or become alarmed at symptoms which a more experienced physician would allow to pass. In such cases the patients might not derive full benefit from the treatment, but as a physician gained confidence and allowed the shocks to go deeper and to last longer, beneficial results should quickly follow. From the patients' point of view the treatment was neither painful nor perilous. Amnesia prevented them from remembering any of their more distressing symptoms. Almost invariably patients began to gain weight and feel more physically fit. This,

together/

together with the return of lucidity more than compensated for any initial discomfort they might have experienced.

Sakel[4] postulated the following theory as to the way in which hypoglycoemia helped cases of schizophrenia; the central nervous system consisted of numerous cells connected by numerous nervous pathways. Some of these pathways were older than others. In schizophrenia, he believed that stimuli ran down the wrong nervous pathways which were newer and produced the wrong type of response. He thought that during the coma period, the nerve cells and pathways were rested and that when the patient awakened, the tendency would be for the nervous stimuli to run along the older pathways and so produce normal reactions and conduct.

Von Pap[48] expressed the belief that the essential cause of the curative effects of insulin was linked, not with the chemical and physiological properties of the insulin, but with the elimination of consciousness during coma, particularly with the dissociation of mental content.

E. Gellhorn[49] stated that hypoglycoemic treatment was successful because it led to excitation of the sympathetica-humeral apparatus through hypoglycoemia of the brain.

Freudenberg[50] stated that insulin therapy was first given empirically and the results obtained seemed to justify its application. Possible "rationales" of the cure were developed later. They were at present not much more than working hypotheses, which might prove of some help in further investigations. Although the metabolic findings in schizophrenia were not absolutely specific, the following hypotheses concerning its basis and the mechanism of cure could be regarded as established. In schizophrenia there was probably a disturbance in cerebral respiration, perhaps due to some lack of oxygenating substances. This disturbance led to a collection of toxic products, probably originating from the protein metabolism. Insulin therapy induced the oxybiotic processes necessary for detoxication and also an irritation of cell membranes, which resulted in an increased exchange between the cells and their surroundings. Improved brain oxidation and the alkalosis occurring during hypoglycaemic coma might be two factors of great importance in the recoveries seen after insulin therapy.

All my patients were given a course of insulin but if improvement did not occur or only reached a certain point, then a course of cardiazol was tried. Reese[27] stated that all his patients were submitted to insulin therapy first. During the

course/

course he decided whether interspersion with, or a change to cardiazol convulsions seemed advisable. When one method failed, a trial at least of the other should be made.

At Whittingham, the room which was used for insulin therapy was also used for the cardiazol treatment. Before treatment was commenced the patients were subjected to a complete physical examination.

Von Meduna and Friedman[25] have divided the contra-indications to treatment into :-

I. ABSOLUTE CONTRA-INDICATIONS.

(a) Organic cardio-vascular disease, whether arterio-sclerotic, hypertensive or inflammatory.

(b) Acute febrile illness.

(c) Pregnancy.

(d) Active tuberculosis.

(e) Abnormality of the blood or urinary constituents determined by complete laboratory examinations.

II. RELATIVE CONTRA-INDICATIONS.

(a) Exopthalmic goitre.

(b) History of severe intracranial injury.

(c) Seropositive syphilis.

(d) Latent tuberculosis.

(e) Confinement to bed for one year before treatment is undertaken.

The technique followed by the author was as follows:-

The patients were not allowed any food after 6 p.m. on the previous evening. Screens were placed round the bed. The initial dose was 4.5 ccs of cardiazol intravenously, if a fit did not occur in 2 minutes a further 3 ccs was given, if again a fit did not occur treatment was abandoned until the next day for injection when 5 ccs. were given. When the convulsive dose was reached it was maintained until I failed to get a reaction. I found that it was important to give the injection as quickly as possible. Von Meduna[51] and Low, Sonenthal, Blaurock, Kaplan and Sherman[52] also emphasised the importance of speed in giving the injection.

After giving the injection, the results observed were as follows. Within a few seconds, the patients face became pale, she usually made an effort to sit up in bed; this was accompanied by several small coughs; the facial expression at this moment was one of great anxiety. Movements of the hands and feet then began, the body fell back on the bed, the patient became unconscious - the whole body stiffened; at that time the mouth opened and remained so for 5-10 seconds; this was the signal to place a gag in the patient's mouth; it was left there until the jaw relaxed. The tonic phase lasted for about 10-20 seconds and was followed by the clonic phase. This

passed/

passed off after about 30 seconds, and the fit was usually over 60-70 seconds after the injection. Brief after twitchings occurred frequently within 30 seconds after the end of the fit. The pupils were found to be widely dilated and unresponsive to light and during the clonic phase an oedematous condition under the lower eyelids was noticed. Increased salivation was noticed at the end of the fit. When the fit was over the patient was very hazy. Within 30 minutes the patient was able to converse, but was exhausted. In 3 hours' time the patients were found to be dull but able to get up and take their midday meal. They were usually rested for 2 days and then given another injection. 15-20 fits were aimed at, but if the patient appeared to have recovered before that time treatment was abandoned.

It was frequently found that an increase in dosage was necessary but in one case the dose was reduced.

PSYCHOLOGICAL OBSERVATIONS.

Prior to the injection, most patients were very frightened; in some cases the fear developed into terror and panic. Patients often begged not to be treated. It was suggested that it was that very fear which was the curative agent in the treatment. Low[52] thought the opposite; in his

series/

series of cases, the patients who subsequently recovered exhibited less fear of the treatment than those who did not recover. In my cases I also found this.

Dynes[53] pointed out that psychotic patients receiving convulsant drug therapy might show undesirable mental sequelae; he noticed two types of undesirable sequelae; firstly one group in which patients became very violent for a prolonged period after receiving convulsant drug therapy and secondly those patients who showed evidence of memory failure, intellectual deterioration and confusion, not present prior to convulsant drug therapy.

Plattner[54] reported seven cases in which there was a memory failure after combined treatment with insulin and cardiazol and attributed the dementia to the fits set up by the latter.

COMPLICATIONS.

In the small number of cases I have done, the only complication I have had was two broken front teeth, this could not be attributed primarily to the treatment, and if a soft absorbent gag as recommended by Von Meduna[25] had been used, then this complication would not have occurred. Other complications recorded were :-

1. DISLOCATIONS.

Jaw dislocations were the commonest, others such as shoulder joint dislocations have occurred. A complete examination was made immediately after the fit. In cases where the jaw became dislocated several times, Von Meduna advised the use of a Barton bandage, placed in position before the injection was given.

2. FRACTURES.

Stalker[55] recorded a case in which, following the convulsion the patient was unable to move and complained of extreme pain in the back. An X-ray revealed a compression fracture of the bodies of the 6th and 7th thoracic vertebrae; there was no evidence of any previous disease of the bone.

Walker and Mayer-Gross[56] reported 2 cases of fractured femur, one uni-lateral and the other bi-lateral. In the first case, the patient had an ankylosed knee and it seemed probable that the anylosis impeded the normal movement of flexion during the fit, and was the main cause of the fracture. In the second case the patient had been in bed for long periods but had been given extra milk, eggs with codliver oil and malt so it was unlikely that he was suffering from

vitamin/

vitamin deficiency. Larkin[67] stated that patients who had cardiazol soon after admission did not have any trouble at all, but patients who had been in hospital for a number of years were apt to have their bones in a bad state due to lack of vitamin D in their diet and fracture occurred almost spontaneously. Those casualties might be avoided by proper vitamins and other diet.

Krause[58] reported several cases of fractured humerus, including one bilateral case.

Parmeijer[59] stated that in 1,200 cases treated with cardiazol there were 15 cases of fracture, most usually of the femur and frequently bilateral.

3. CARDIO-VASCULAR COMPLICATIONS.

Dick and McAdam[60] reported four cases of auricular fibrillation or acute heart block occurring shortly after the injection and persisting for a period ranging from hours to days.

4. PULMONARY COMPLICATIONS.

Parmeijer[59] in his series of cases reported 7 of pulmonary abscess. Von Meduna[25] recorded a 0.1% occurrance of pulmonary abscesses in his cases. He thought the condition

was/

was due to aspiration, inflation and transitory pulmonary oedema during the fits, and recommended that the treatment be only given to healthy people free from cardiac and respiratory disease of any type and that an absorbent gag made of cellucotton be used to absorb the orotracheal secretions. Another precaution was to give the treatment only if the stomach was empty to avoid the aspiration of regurgitated material.

5. CAMPHOR POISONING.

Von Meduna[25] noted one case of non-fatal and two of fatal acute camphor intoxication. In these cases the patients displayed extreme lassitude, the pulse and respiratory rate became increased, persistent leaden cyanosis was noted and physical examination revealed some bronchiolar or pulmonary inflammation. He recommended the use of the oxygen tent and intravenous administration of hypertonic glucose solution.

Von Meduna[25] stated that the fundamental basis of the convulsive irritative therapy was the statistically significant biologic antaganism between the epileptic state and schizophrenia. Also, he thought that medullary irritation with resultant respiratory, vasomotor and autonomic responses was the basis of the cardiazol convulsive therapy.

Schmidt and Cobb[61] reported that the action of carbon dioxide on the central nervous system was that of vasodilation and circulatory stimulation in order to provide more oxygen to more brain tissue by enlarging the vascular bed and volume of blood in the brain. Von Meduna[25] thought that this might possibly be the basis of the transitory improvement noted in schizophrenia after inhalation of carbondioxide, and went on to say that if the underlying action of cardiozol was in part that of dilatation of the blood vessels of the brain, the mechanism of influence would be similar to that of carbondioxide but more profound, in addition there was also a direct stimulating action on the cells of the central nervous system.

Gellhorn[49] reported that cardiozol led to an excitation of the sympathetico-adrenal system of a strong and lasting type and so produced a profound alteration in the metabolism of the brain.

Friedman[62] postulated the possibility of a chemical detoxifying process because the drug was foreign to the body, and when given in large doses, might in the process of elimination, bring about chemical union and metabolism of fixed or spell-bound toxic agents that would be eliminated from the body in combination with the drug.

IV. C A S E S.

(1) E.K. Single. Aged 31 yrs. Admitted June 22nd, 1938.

Before treatment.

After treatment.

OCCUPATION. Novice.

HEREDITY. No history of mental illness in ascendants. The patient's mother and father were cousins.

PERSONAL HISTORY. She had an apparently normal childhood, she was the thirteenth child in a family of fourteen. She did well at school and was described as a popular girl, good at games. After leaving school she took a secretarial course and did some secretarial work, but was never at one job long. At various periods, she worked at home on the farm and did some domestic service. In January 1937, she entered a convent.

PRE-PSYCHOTIC PERSONALITY. Her sister, who was the only relative I ever interviewed (the others were in Ireland) described the patient as industrious, capable but easily upset by criticism. She did not make friends easily, preferred the company of her own family to any outsiders. She was always deeply religious and eventually decided to enter a convent as a novice.

HISTORY of PRESENT ILLNESS. In January 1938, it was noticed in the convent that the patient was neglecting her religious duties. She frequently lay in bed and refused to get up. When spoken to she refused to answer, occasionally she was found wandering about the convent in an aimless manner. In March she attempted to escape from the convent but was brought back, a short period of apparent normality followed this episode, but in June she was taken to a nursing home as she refused food completely. Later the same month she was admitted to Whittingham.

On admission she was thin and very pale, no organic disease was found. W.R. was negative, C.S.F. report was negative. Mentally she appeared confused, did not converse but remained silent when spoken to. She was resistive to nursing attention and frequently struck out at the nurse. She tore up her bedclothes. Her habits were faulty. She

refused/

refused food, had to be spoonfed and occasionally tubefed.

The following notes indicated her progress in hospital.

JULY 20th 1938. "She is dull, impulsive at times, lies in bed staring into space. Occasionally answers a question with a monosyllable but more often refuses to speak."

AUGUST 31st 1938. "There is no improvement, she is idle, has no external interests, seldom speaks. She is still difficult with her food."

OCTOBER 14th, 1938. "She is dull and apathetic, still occasionally refuses her food. She stands in the same position all day and occasionally strikes out impulsively."

DECEMBER 13th, 1938. "She refused to speak at all this morning and was very resistive while a physical examination was being carried out. She refuses to co-operate and has never occupied herself since admission. She is often to be seen smiling in a silly fashion to herself.

Insulin treatment was commenced on January 5th 1939 with a dose of 15 units. The dose was increased by 5 units per day until at 60 units on January 19th she had her first coma; this was a typical wet coma. During

the/

the whole of treatment, she continued to react to insulin with a quiet wet type of coma.

On January 27th her coma dose had been dropped to 50 units, she had a sixty minutes coma, her seventh and at 11-40 a.m. when she came round, she answered questions readily and said she was feeling a good deal better. Next morning at 7-30 a.m. she refused to say Good Morning.

On February 4th she was given 55 units at 7-30 a.m., she lay very quiet in bed, began to perspire at 10-10 a.m. and was judged to be in coma at 10-35 a.m., her pupils were contracted. At 11-5 a.m. she was in deep coma, she was perspiring freely and salivating profusely; at 11-20 a.m. there was an extensor response to the plantar reflex and a diminished response to the Tendon reflexes. Glucose was given at 11-30 a.m. and at 12 noon she was fully conscious. At 12-15 p.m. she said she felt very well and thought that the treatment was doing her a great deal of good.

On February 5th the patient was menstruating, no insulin was given, a mental note said "This patient is improving, she answers all questions readily and can carry on a rational conversation. She is taking her food well, appears

to/

to be interested in her surroundings, works hard in the ward. She does not readily start a conversation herself."

On February 22nd she had 50 units at 7-40 a.m. After lying quietly until 9-40 a.m. she had a severe fit. Glucose was given nasally at 9-45 a.m. At 10-0 a.m. she was quite conscious and able to answer questions. At 12-30 p.m. she became drowsy again and vomited. 1 cc of adrenaline was given and she came round slowly. I believed that this fit was the result of an overdose and also thought afterwards that an intra-venous injection of glucose instead of the adrenaline should have been given.

After this point I found that the patient appeared to become more sensitive to insulin, her coma dose gradually became smaller and she tended to take a long time to come round. The dose was gradually reduced to 15 units on March 25th. when she had a light coma. Treatment was then stopped, in all she had forty seven comas. At this point, the patient appeared to have recovered, she had regained her insight and realised she had been mentally ill. She conversed readily with the staff and other patients, her conduct was exemplary. She was interested in her appearance and kept herself clean and tidy.

A fortnight later the patient had relapsed somewhat, she was pre-occupied, appeared drowsy and had stopped talking unless spoken to, when however, her conversation was quite rational.

It was decided to give her some Cardiazol, three injections were given, 4.5 ccs in each, a fit occurred each time and the patient brightened up considerably and appeared like she was after she finished her course of insulin.

She was left now to see how she went on. She kept well until discharged on May 26th. For the rest of her time at hospital she was bright and cheerful, showed plenty of initiative, she even sang solo songs for the other patients. She realised she had been ill mentally and was very grateful for her treatment.

She was asked if she had any unpleasant sensations following the insulin, she said that all she remembered was the prick of the injection in the early morning. Regarding the cardiazol, she definitely disliked it and said that she felt her chest was going to burst.

OBSERVATIONS of PUPIL CHANGES DURING HYPOGLYCAEMIA.

Many pupil measurements were made, all by the author so that each measurement was comparative to any other; at the same time other observations were made. The measurements and observations were made in the following manner.

Metal cages were constructed which could be fitted to the head of any of the ward beds; a black cloth was fitted round this cage so that the observer inside the cage could watch the patient's pupils with all external light excluded. In order to minimize the effect of the light reflex a constant light was used for all the measurements; this consisted of a 15 watt bulb in an inspection bracket wrapped in several thicknesses of yellow tissue paper. This lamp was fixed on the metal framework at a given point and the patient was always placed so that her observed eye was the same distance from the lamp. This lamp was just sufficient to permit observation of the pupil and consequently allowed dilatation of the normal pupil to about the midsize position 6.5-8 mms.

The effect of accommodation was minimised by getting the waking patient to look towards the roof of the cage apparatus. Measurements during coma were taken as far as

possible/

possible when the eyes were in the same position. Measurements were made at irregular times in order to observe the pupils at all stages of the hypoglycaemia from before the injection to recovery of consciousness. Observations made at the same time were just as important as the measurements were. In order to get a true pupil reading, it was necessary to adopt a special technique, namely, the observer sat beneath the tent formed by the black cloth draped on the metal cage; he rested his hand on the patient's forehead so that with his forefinger he could raise the upper lid and observed the pupil without disturbing the patient.

PUPIL OBSERVATIONS.

(1) 15.2.39.

TIME	SIZE.	OBSERVATIONS.
7.30 a.m.	7.0 mms.	
9.0 a.m.	6.5 mms.	
9.40 a.m.	7.0 mms.	Drowsy.
10.0 a.m.	6.0 mms.	Commencing coma, perspiring.
10.25 a.m.	5.0 mms.	Deepening coma.
11.0 a.m.	4.0 mms.	Deep coma, perspiring and salivating.
11.15 a.m.	4.0 mms.	Deep coma.
11.50 a.m.	7.0 mms.	Awake after nasal feed.

(2) 17.2.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.0 mms.	
9.0 a.m.	7.0 mms.	
9.30 a.m.	6.0 mms.	Drowsy, perspiring.
10.0 a.m.	5.0 mms.	Commencing coma.
10.30 a.m.	3.5 mms.	Deepish coma.
11.15 a.m.	3.5 mms.	Deep coma.
11.50 a.m.	7.0 mms.	Awake after nasal feed.

(3) 18.2.39.

TIME.	SIZE.	OBSERVATIONS.
9.30 a.m.	7 mms.	Drowsy.
10.0 a.m.	5 mms.	Commencing coma, perspiring.
10.40 a.m.	3.5 mms.	Deep coma, face was slapped, pupils dilated up to 8 mms. after a latent period of 1-2 secs. at same time pulse rate increased, after a further 10-20 secs. the pupils again contracted.
11.0 a.m.	3.0 mms.	
11.45 a.m.	6.5 mms.	Awake after nasal feed.

(4) 20.2.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.5 mms.	
9.0 a.m.	7.0 mms.	
9.30 a.m.	7.0 mms.	Drowsy.
10.0 a.m.	5 mms.	Commencing Coma, perspiring.
10.35 a.m.	3.5 mms.	Deep Coma, perspiring freely.
11.0 a.m.	3.0 mms.	Salivating profusely.
11.40 a.m.	7.0 mms.	Awake after nasal feed.

(5) 21.2.39.

TIME.	SIZE.	OBSERVATIONS.
9.0 a.m.	7 mms.	
9.25 a.m.	7 mms.	
10.0 a.m.	4.5 mms.	Commencing coma, perspiring.
10.30 a.m.	4.0 mms.	Deep coma, perspiring, salivating.
11.0 a.m.	3.0 mms.	Deep coma. Following a stimulus the pupils dilated up to 8 mms. after a latent period of 1-2 secs., the pulse rate quickened; after about 20 secs, the pupils again contracted and the pulse rate slowed.
11.55 a.m.	7.5 mms.	Awake after nasal feed.

(6) 22.2.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	8 mms.	Slight twitching of facial muscles.
9.30 a.m.	8 mms.	Twitching continued.
9.40 a.m.		Severe fit, during the fit the pupils were widely dilated, towards the end of the fit they became contracted to 5 mms. for about 2 minutes, then gradually dilated up to 7 mms.

(7) 24.2.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.5 mms.	
9.0 a.m.	7.5 mms.	
9.45 a.m.	7 mms.	Drowsy.

(7) Contd.

TIME.	SIZE.	OBSERVATIONS.
10.15 a.m.	6 mms.	Early coma, perspiring.
10.50 a.m.	4 mms.	Deep coma, perspiring freely and salivating profusely.
11.40 a.m.	7 mms.	Awake after nasal feed.

(8) 25.2.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	6 mms.	
9.50 a.m.	5 mms.	Early coma.
10.30 a.m.	3 mms.	Deep coma, perspiring freely, salivating, slow pulse 52.
11.0 a.m.	3 mms.	
11.45 a.m.	7 mms.	Awake after nasal feed.

(9) 27.2.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.5 mms.	
9.10 a.m.	7 mms.	
10.0 a.m.	6 mms.	Drowsy.
10.30 a.m.	4 mms.	Deep coma.
11.0 a.m.	3 mms.	Deep coma.
11.25 a.m.	Nasally fed.	
12.0 noon	5 mms.	Only partially conscious, 25 ccs. of 33 1/3% glucose solution given intravenously.
12.15 p.m.	8 mms.	Quite wide awake.

(10) 28.2.39.

TIME.	SIZE.	OBSERVATIONS.
10.0 a.m.	5 mms.	Early coma, perspiring.
11.0 a.m.	3 mms.	Deep coma, a slap on face made pupils dilate up to 8 mms. after latent period of 1-2 secs, after 20 secs. pupils contracted again.
11.40 a.m.	7 mms.	Awake after nasal feed.

(11) 15.3.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	7 mms.	
9.45 a.m.	6 mms.	Drowsy.
10.15 a.m.	5 mms.	Early coma, perspiring.
10.45 a.m.	4 mms.	
11.5 a.m.	3 mms.	Deep coma, perspiring, salivating, slow pulse 56.
11.55 a.m.	6.5 mms.	Awake after nasal feed.

(12) 20.3.39.

TIME.	SIZE.	OBSERVATIONS.
9.0 a.m.	7 mms.	
9.30 a.m.	7 mms.	Drowsy.
10.0 a.m.	4.5 mms.	Early coma, perspiring.
10.30 a.m.	3 mms.	
11.10 a.m.	3 mms.	Deep coma, perspiring freely and salivating profusely.
12.0 noon.	7 mms.	Awake after nasal feed.

This patient passed into coma quietly with no restlessness and from the readings it was seen that as coma developed and deepened there was a gradual diminution in the size of the pupils. After feeding nasally with glucose and when the patient was awake, the pupils were found to return to their normal size. An interesting point was that if the patient was stimulated during deep coma whilst the pupils were contracted; the pupils dilated after a latent period of 1-2 secs., remained so for about 20 secs. and then contracted again. A further stimulation produced a further dilatation. Associated with this dilatation was a quickening of the pulse which also later slowed down. During the period of deep coma in this patient, the pupils were contracted, the pulse was slow, there was free perspiration and salivation was profuse. The salivation did not become profuse until the patient was in deep coma.

BLOOD SUGAR OBSERVATIONS.

The micro-method of Folin Wu, using .1 cc of capillary blood was used. The principle of this method is as follows; the protein-free filtrate is heated with an alkaline cupric tartrate solution under standard conditions. It is then treated with a solution of phosphomolybdic acid, which is

reduced/

reduced in proportion to the amount of cuprous salt, and therefore, in proportion to the quantity of sugar. The compound formed by the reduction of phosphomolybdic acid is blue, and the intensity of this colour is compared in a colorimeter with that of a standard solution of pure dextrose similarly treated.

A blood sugar tolerance test and four graphs of the blood sugar following insulin are shown. Interesting points were :-

(1) The greatest fall in the blood sugar took place in the first one and a half hours, when apart from drowsiness, there were no symptoms.

(2) The commonest level for coma appeared to lie between 20-35 mgms. per 100 ccs.

(3) After the nasal feed, the patient was quite conscious and yet her blood sugar was not as high as the fasting level at which she started.

(4) In the course of treatment, this patient developed the well known sensitization to insulin so that towards the end of treatment, with a smaller dose of insulin, the blood sugar fell just as much as it did at the beginning with larger doses.

PULSE RATE OBSERVATIONS.

Pulse rates were taken every day at half hourly intervals from 7.30 a.m. to 1.30 p.m. Six records of this particular patient are shown. The points to be noticed were the initial tachycardia after the injection of insulin; with the onset of a quiet wet type of coma, which was usual for this patient, a bradycardia developed; at this point the patient was perspiring freely, salivating profusely and the pupils were contracted. If the patient was stimulated in ways varying from a slap on the face to merely sitting on the bed it was found that the pulse rate quickened and then slowed down, concurrent with this was a dilatation of the pupils which later contracted.

BLOOD PRESSURE OBSERVATIONS.

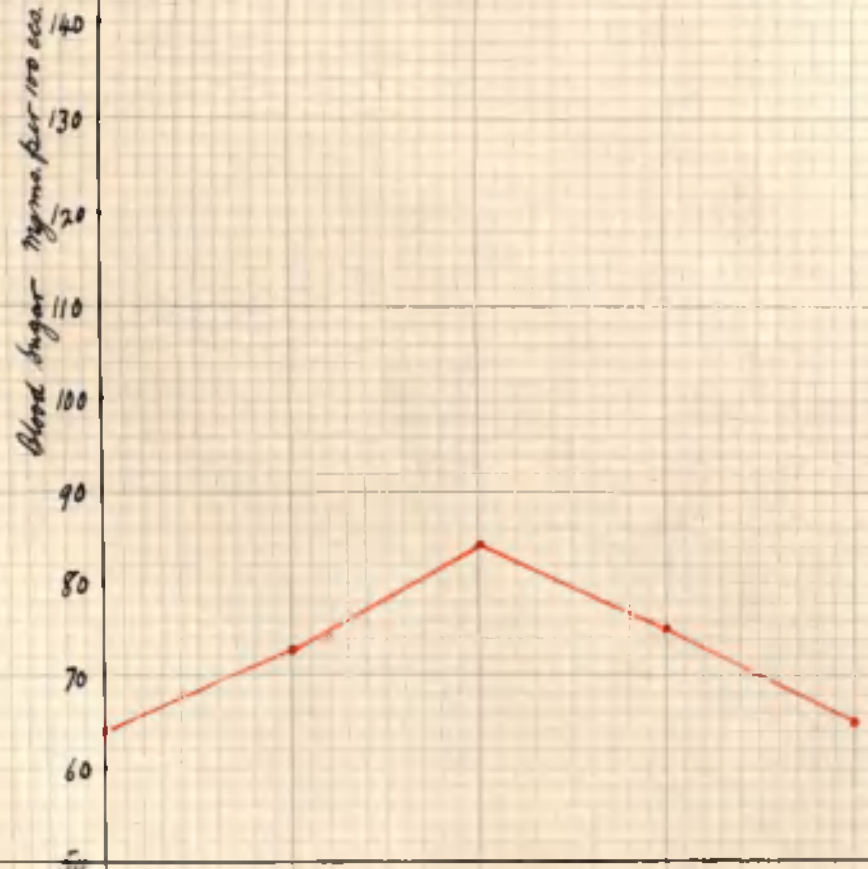
Five graphs of the systolic and diastolic pressures are shown following the injection of insulin, all were taken with the patient lying down. In this patient, the systolic and diastolic readings tended to rise in the early phase of hypoglycaemia but fell as coma developed, the diastolic fell more than the systolic. The pulse pressure was increased. The readings taken on January 26th 1939 were interesting in

that/

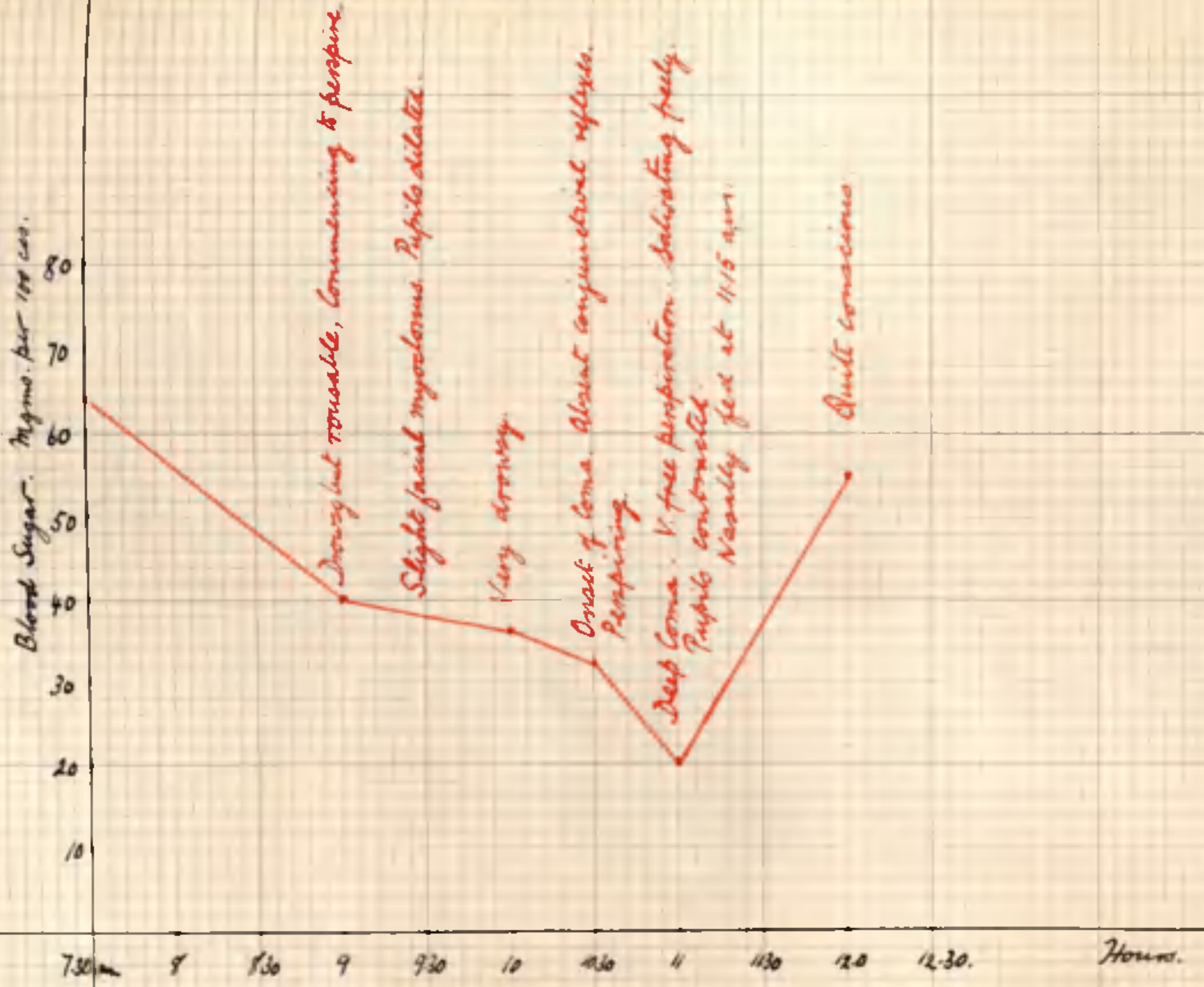
that at 11 a.m. during deep coma, the diastolic reading fell to 0; after nasal feeding, it was found to have risen again by 11.30 a.m. This patient perspired very freely and it seemed possible that this very free perspiration resulted in a marked dehydration of the blood. I noticed this several times in this patient and also found it in other patients who perspired very freely during coma.

A weekly weight graph was made for each patient during treatment, in this patient the greatest rise occurred in the first two weeks, but the graph showed an upward curve all through treatment.

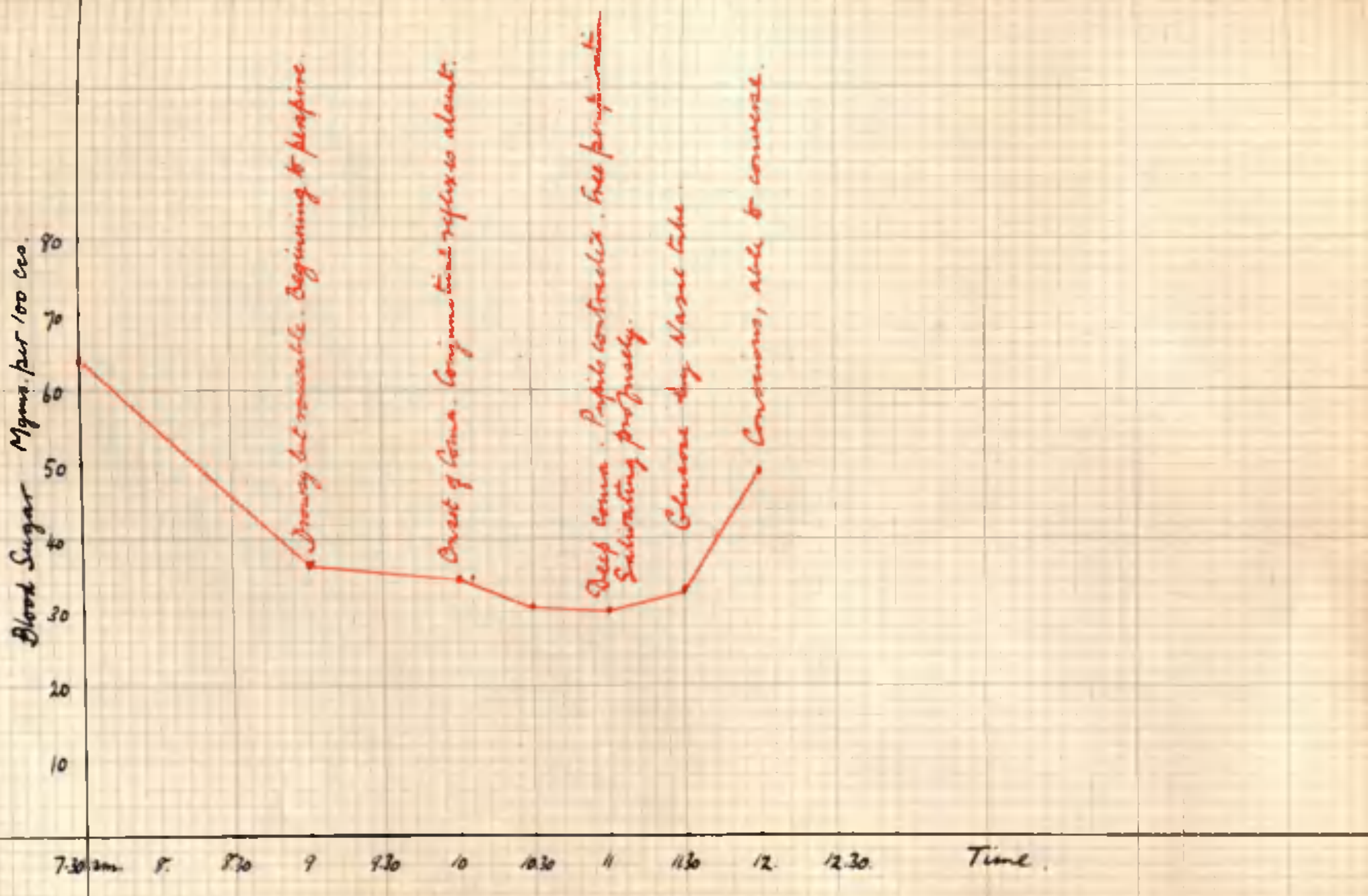
Patient E.K. Date 3.1.39. Blood Sugar Tolerance Test.

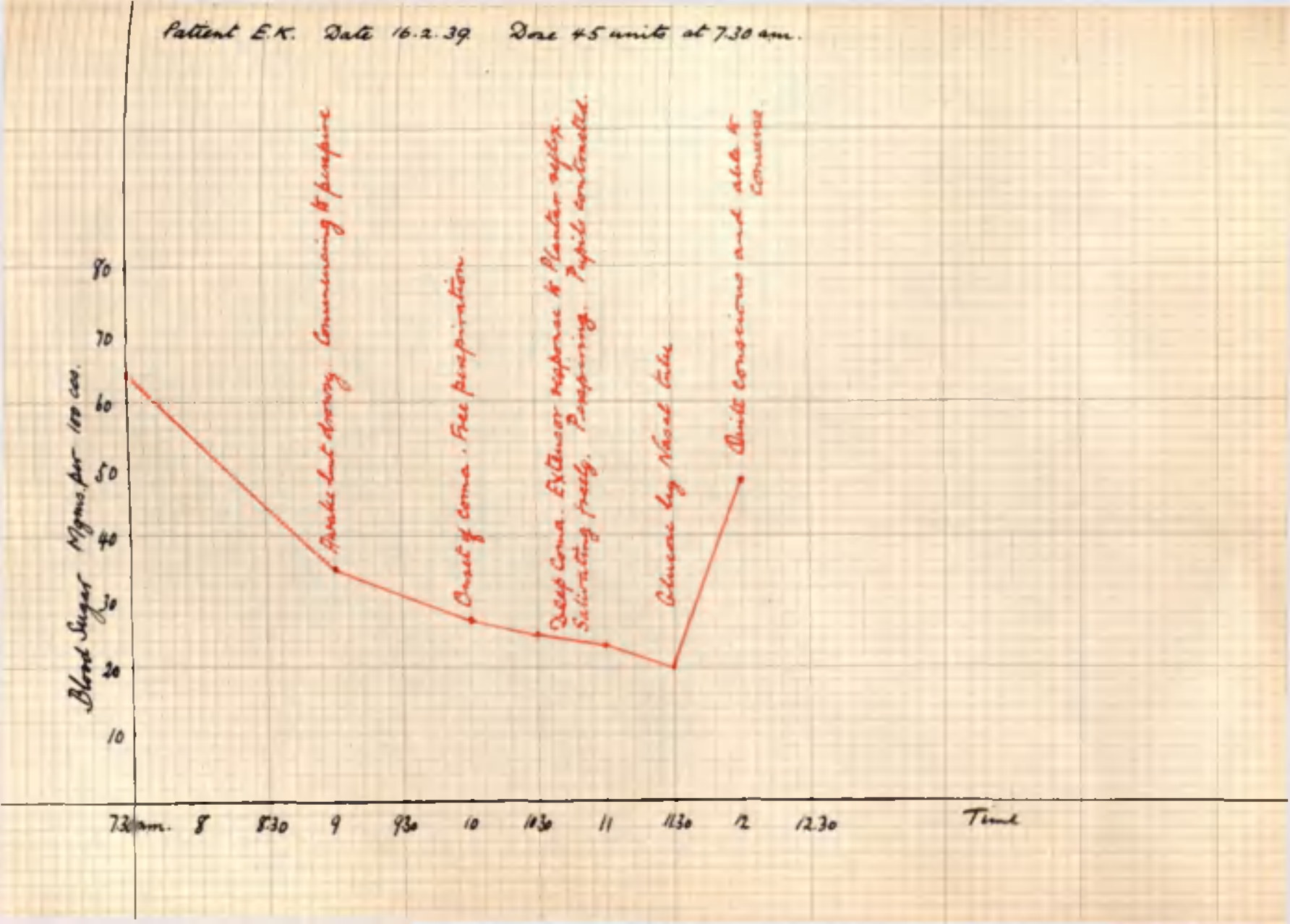


Patient E.K. Date 23.1.39. Dose 55 units at 7.30 a.m.

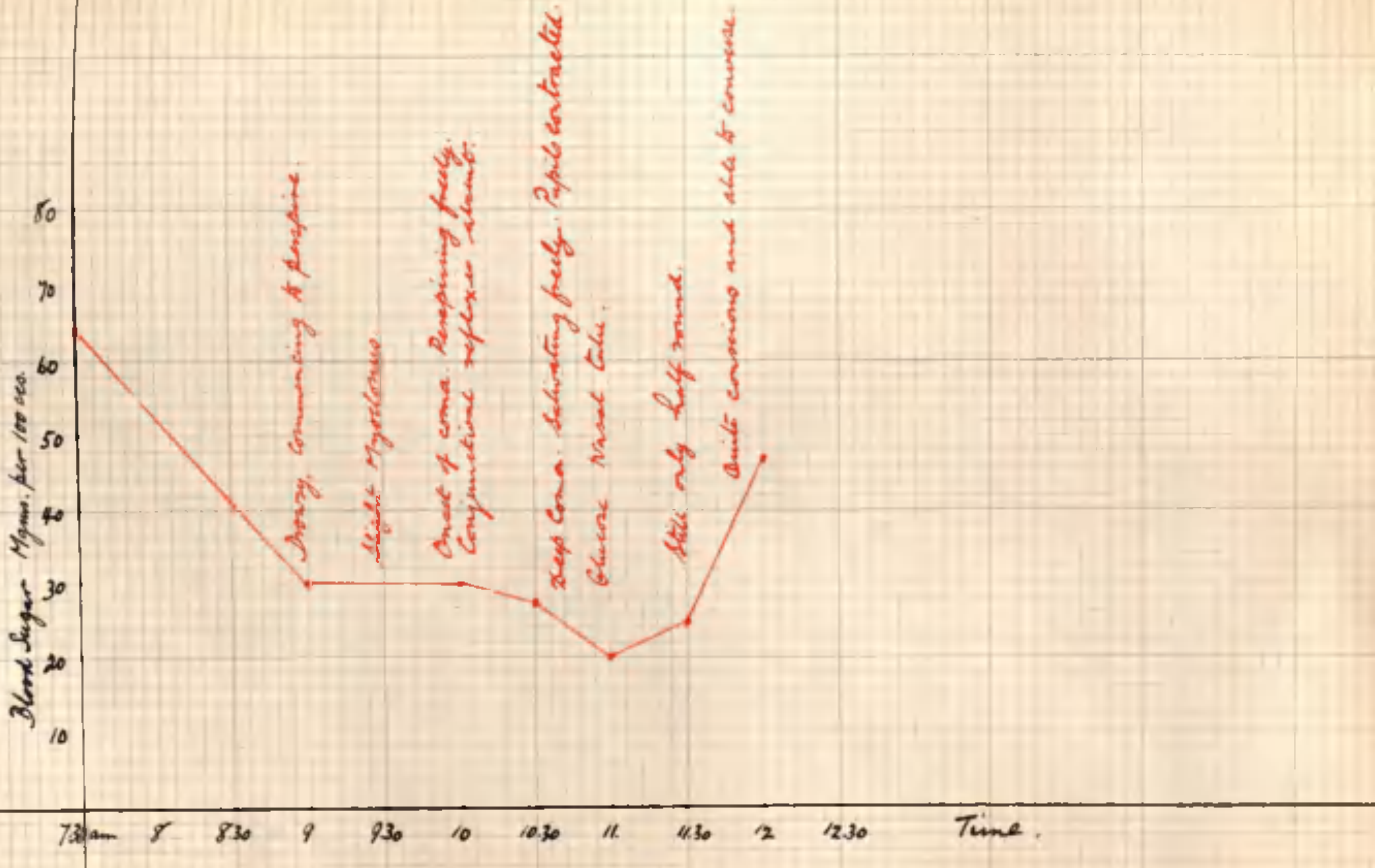


Patient E.K. Date 3.2.39. Dose 55 units at 7.30 a.m.




Patient E.K. Date 16.2.39 Dose 45 units at 7.30 am.
Blood Sugar Mgms. per 100 cc.
80
70
60
50
40
30
20
10
Faint but definite. Commencing to perspire
Coma. Free perspiration
Deep Coma. Eyeballs soft. Reflexes & Plantar reflex. Salivating freely. Perspiring. Pupils contracted.
Glucose by Nasal tube
Quite conscious and able to converse
7.30 am. 8 8.30 9 9.30 10 10.30 11 11.30 12 12.30
Time

Patient E.K. Date 10.3.39. Dose 35 units at 7.30 am.



4 HOUR CHART.

DISEASE

Name { E.K.

Age

Diet

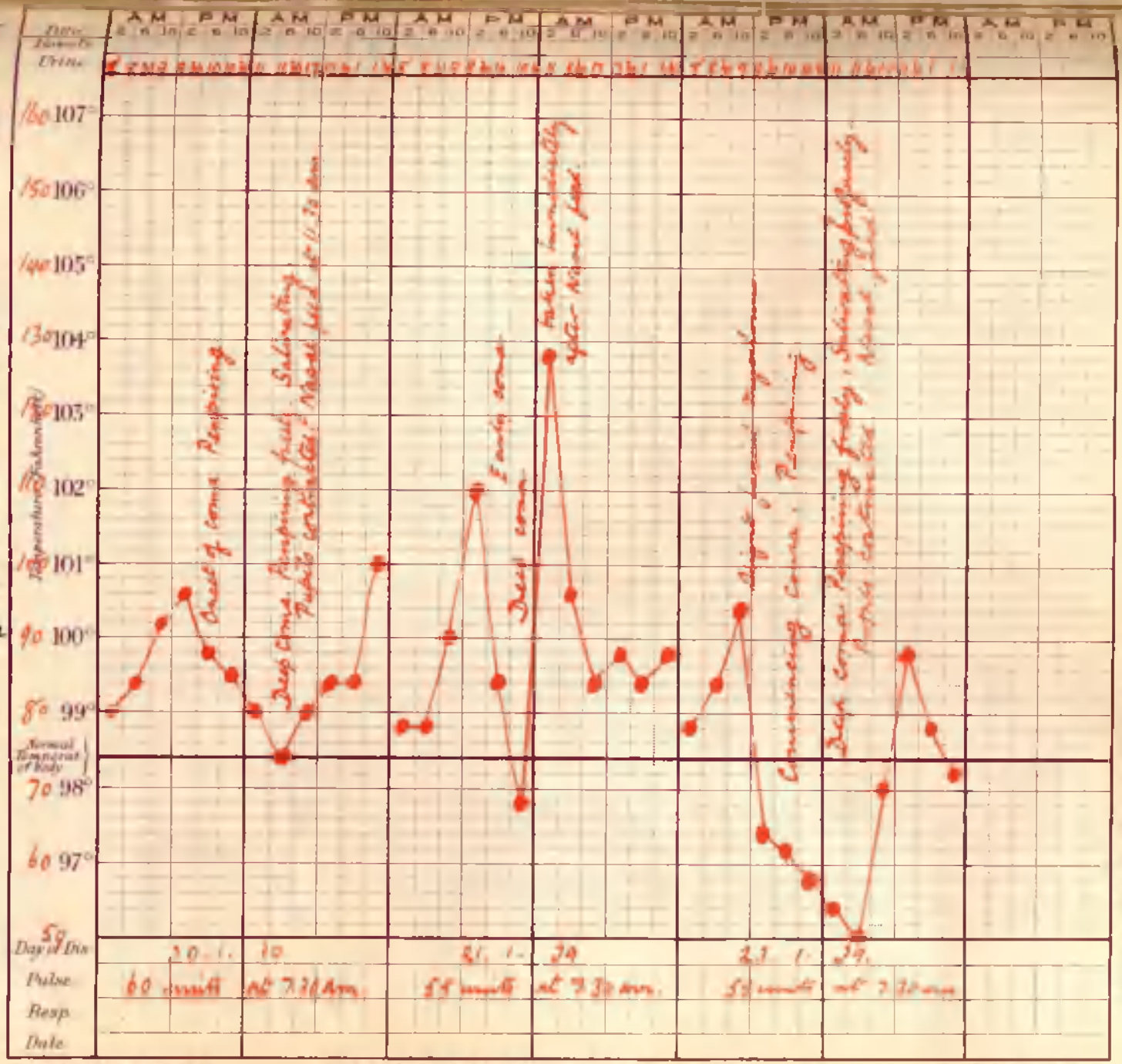
Case Book N°

Notes of Case

Three pulse records of the same patient showing the initial speeding up of the pulse and then the development of bradycardia as a quiet wet type of coma developed.

Date of admission

Result



Entered at Stationers Hall Printed and Published by Waddington & C.ts Date Street, Kingsway W.C. Lewis's Clinical Chart.

4 HOUR CHART.

DISEASE

Name E. K.

Age

Diet

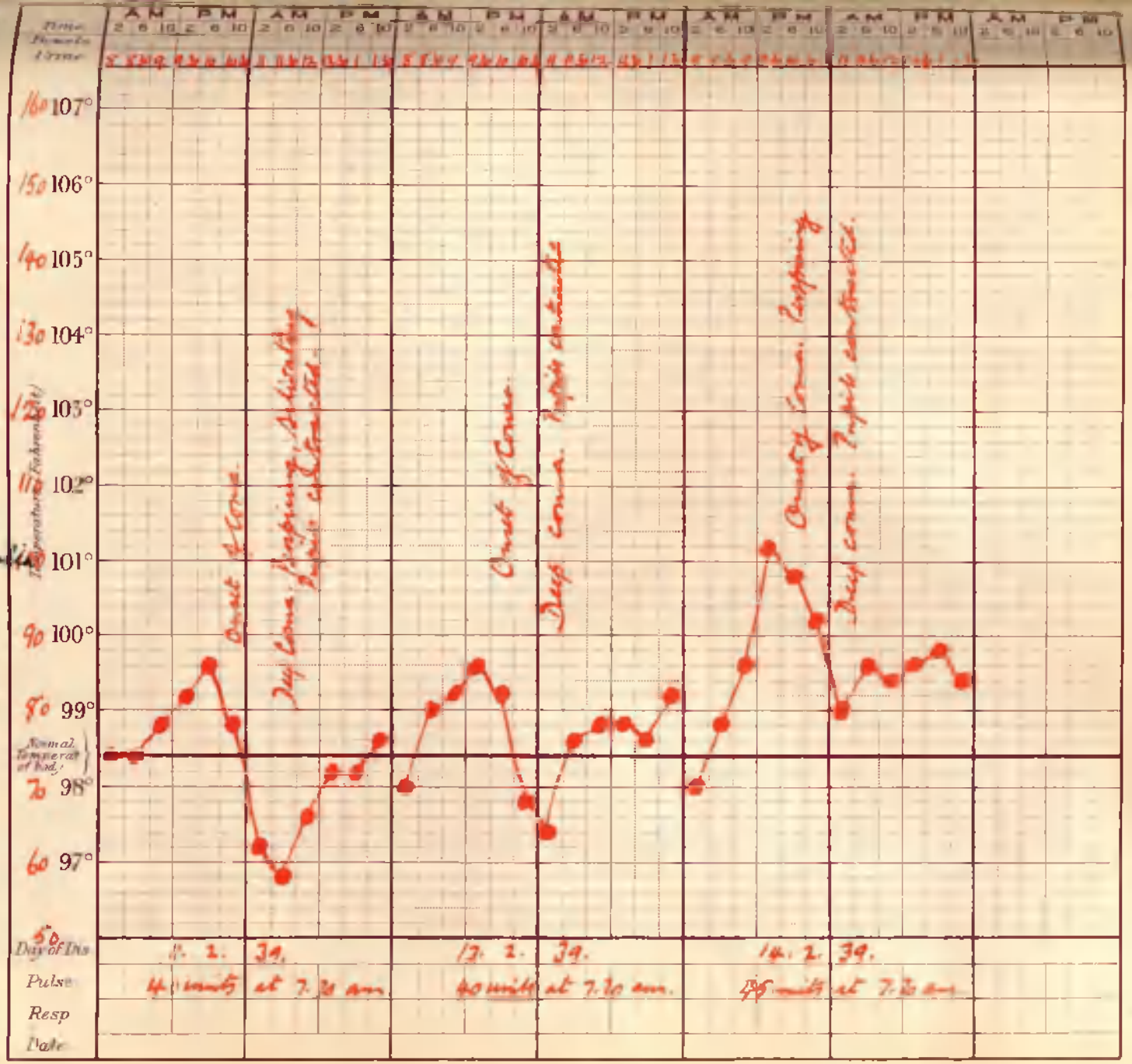
Case Book No.

Notes of Case

Three more pulse records showing the initial tachycardia followed by a bradycardia as a quiet wet type of coma developed.

Date of admission

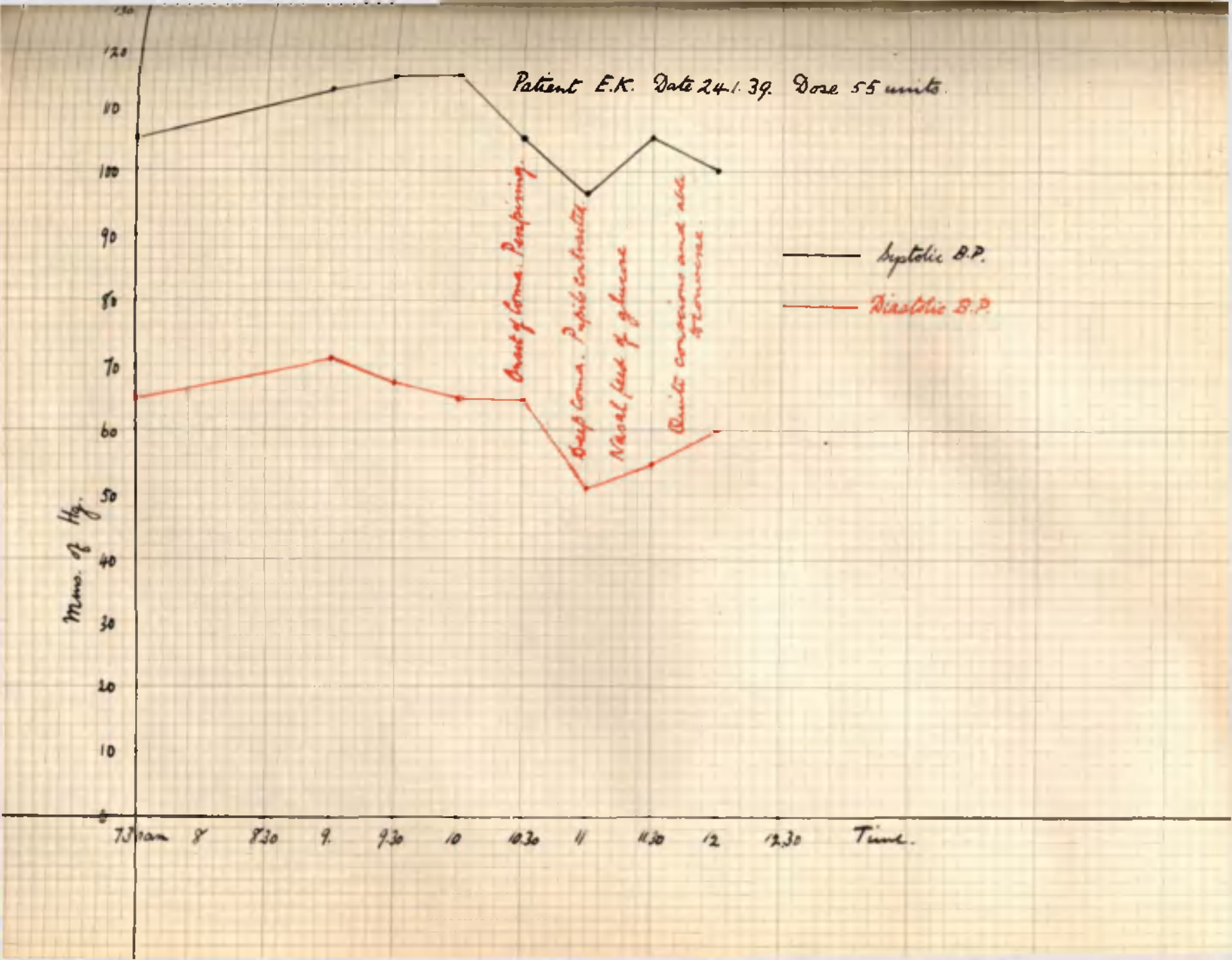
Result

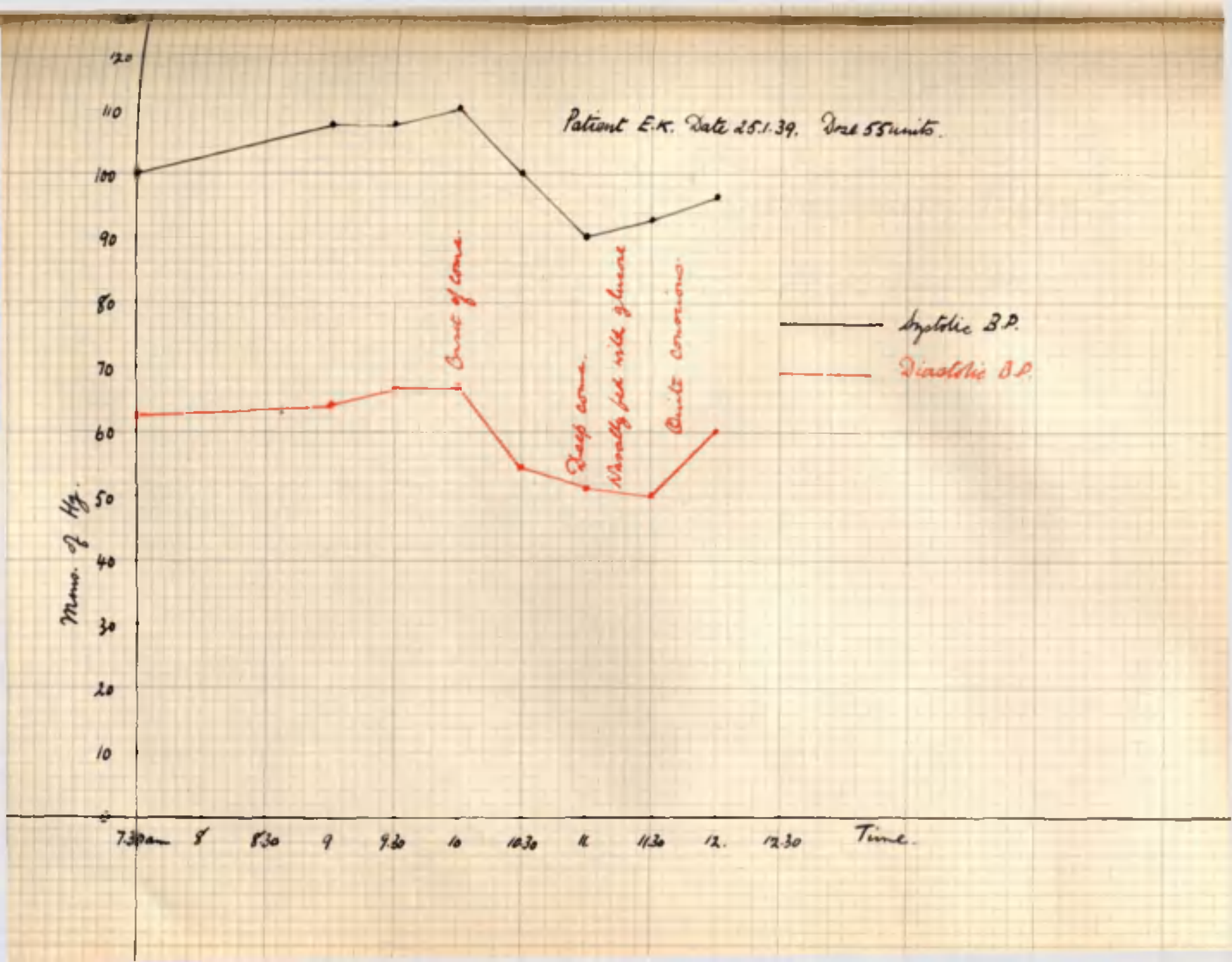


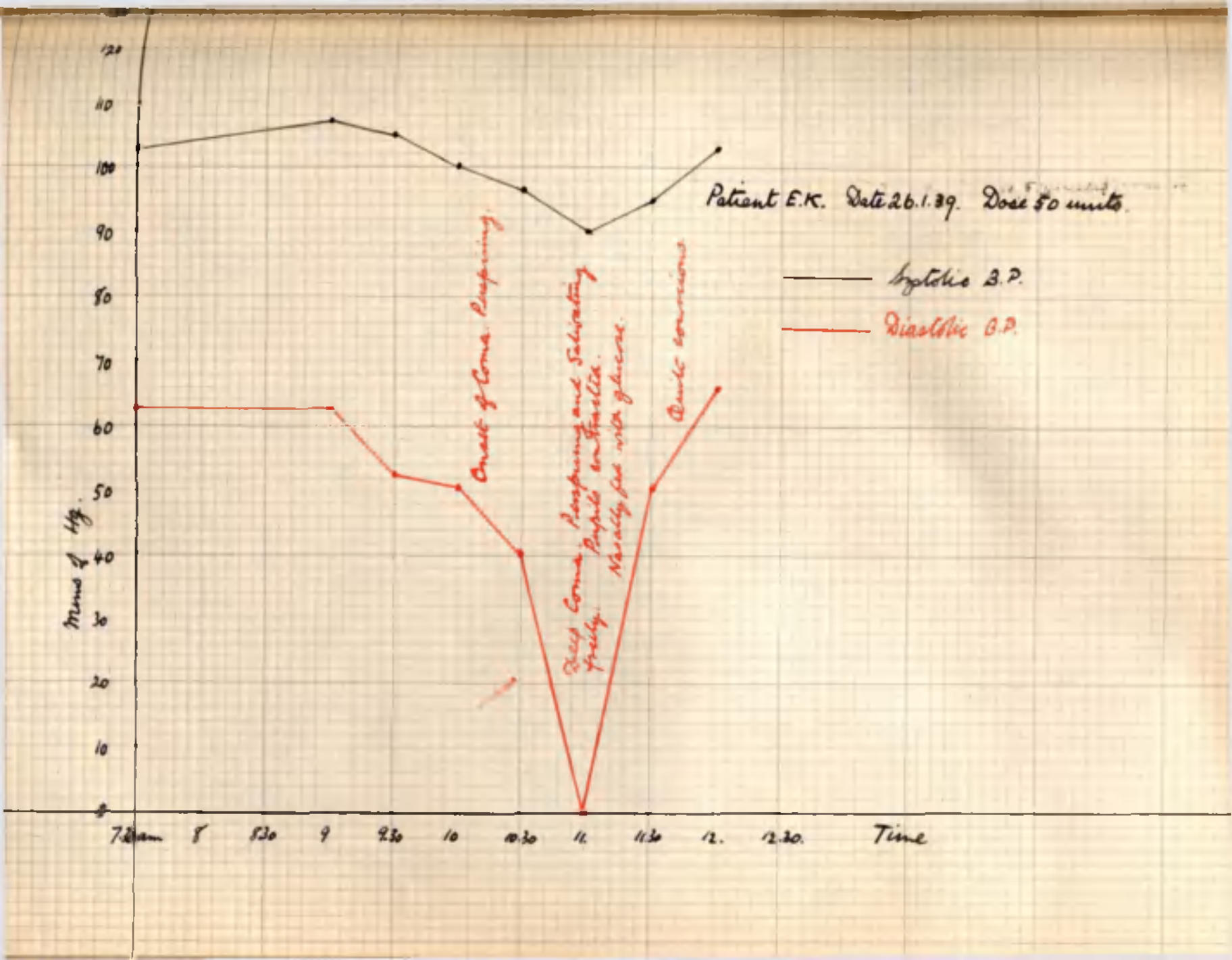
Entered at Stationers Hall

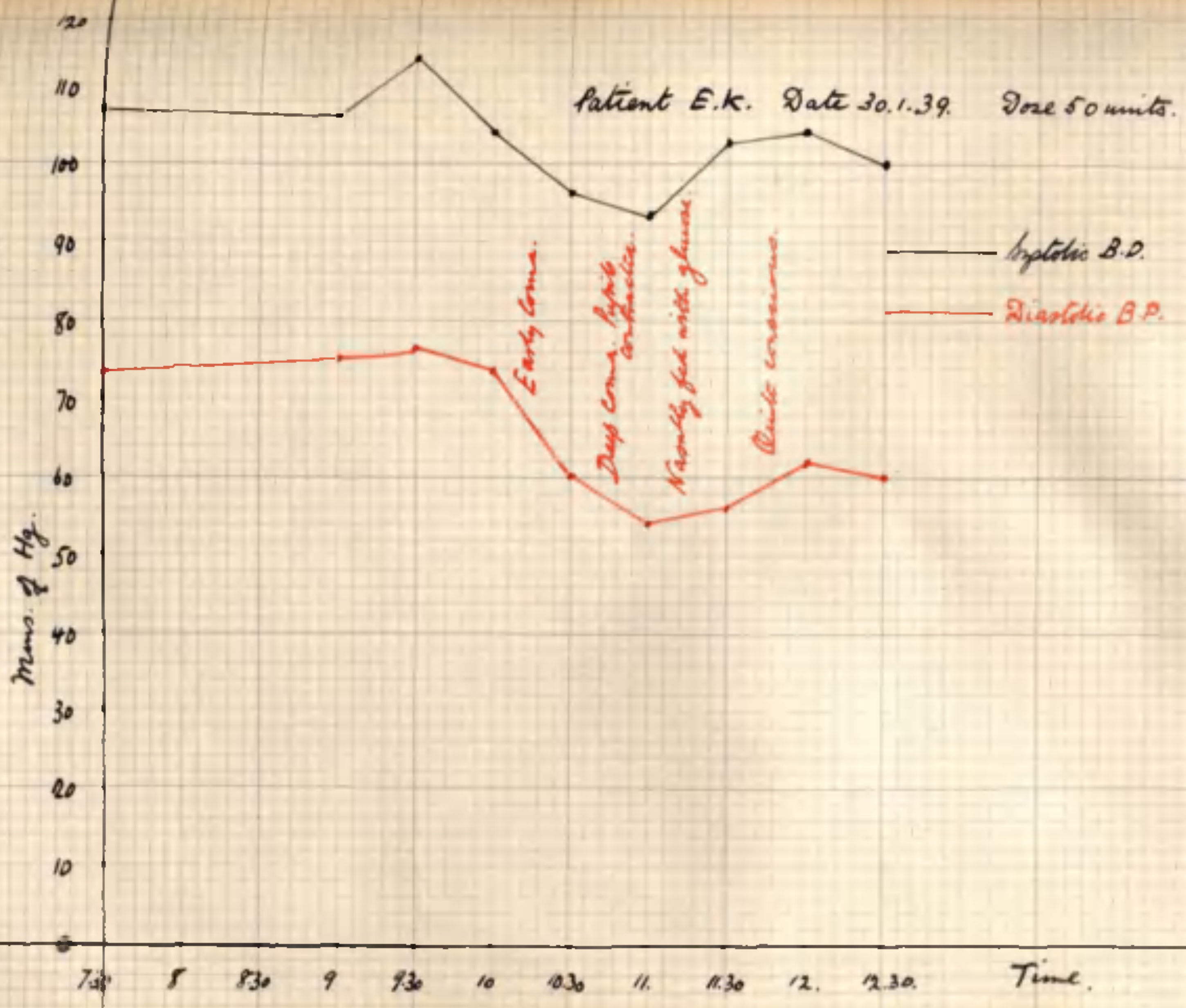
Printed and Published by Wodderspoon & Co Ltd Gate Street Kingsway W.C.

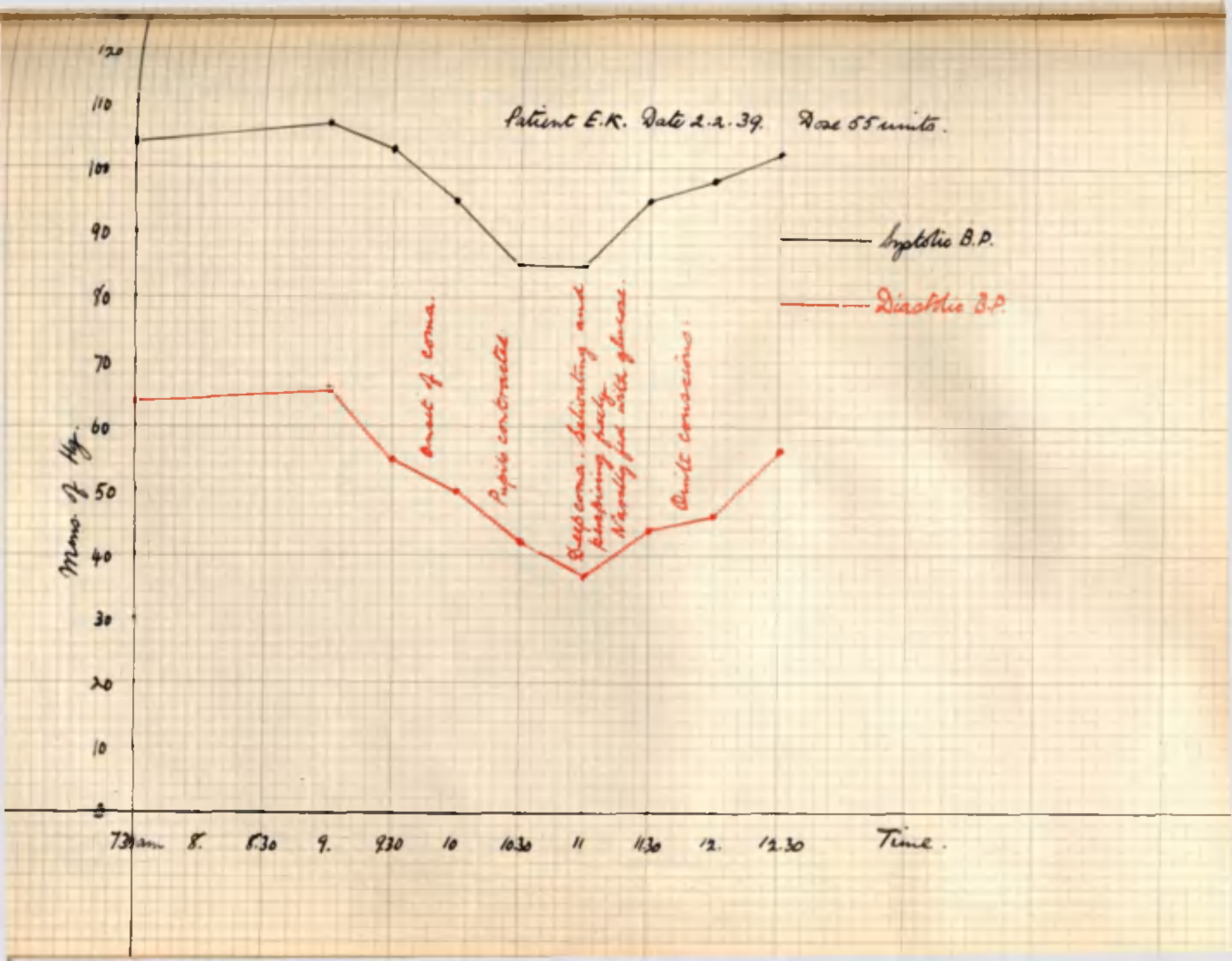
Goulds Clinical Chart


Patient E.K. Date 24.1.39. Dose 55 units.
Systolic B.P.
Diastolic B.P.
Onset of coma. Perspiring.
Deep coma. Pupils contracted.
Nasal feed & glucose
Quite conscious and ate strawberries.
Mms. of Hg.
0
10
20
30
40
50
60
70
80
90
100
110
120
130
7.30 am
8
8.30
9.
9.30
10
10.30
11
11.30
12
12.30
Time.

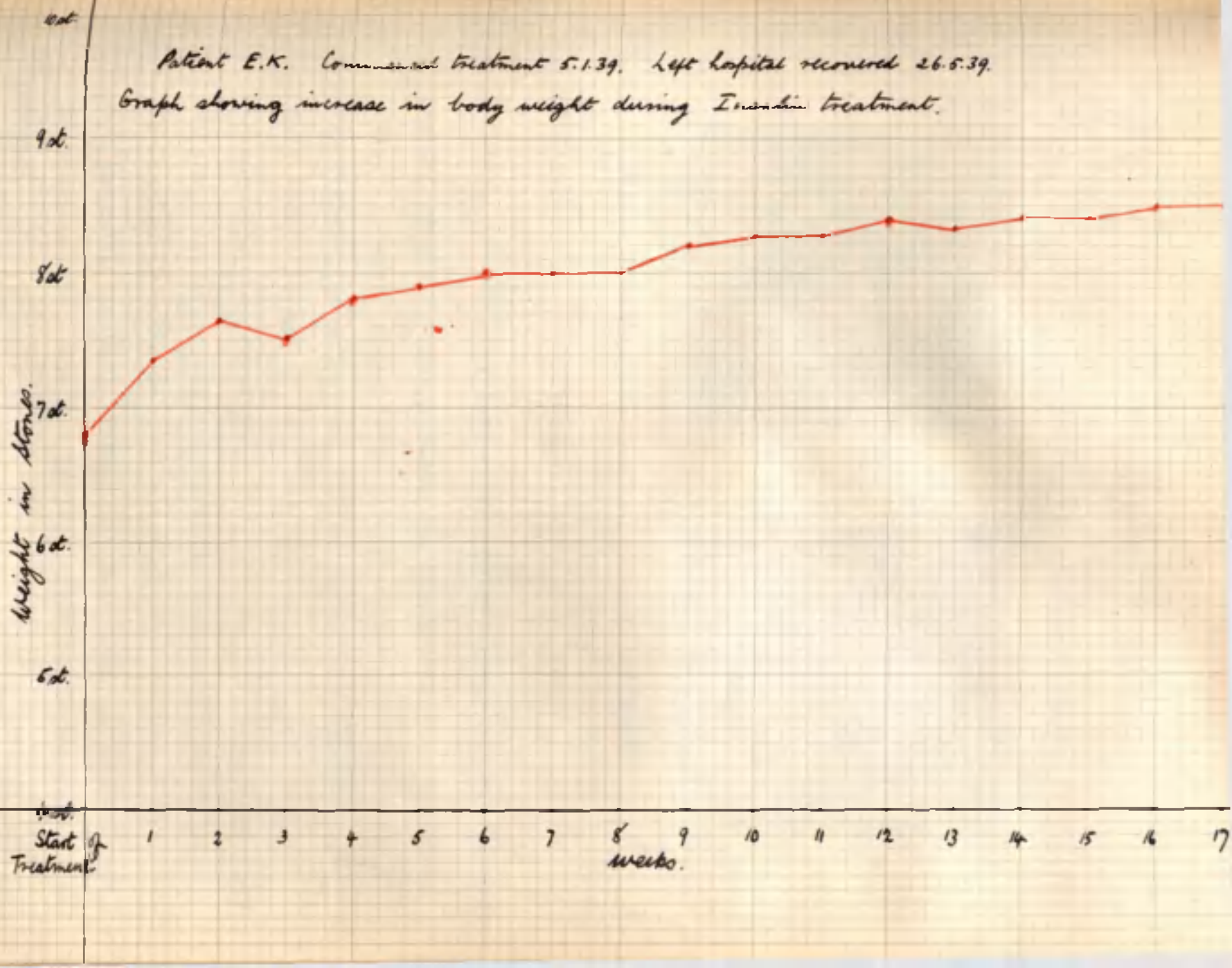

Patient E.K. Date 25.1.39. Dose 55 units.
Onset of coma.
Deep coma.
Normality just with glucose
Quite conscious.
Systolic B.P.
Diastolic B.P.
Mms. of Hg.
120
110
100
90
80
70
60
50
40
30
20
10
0
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12.
12.30
Time.


Patient E.K. Date 26.1.39. Dose 50 units.
Systolic B.P.
Diastolic B.P.
Onset of Coma. Sleeping
Deep Coma. Perspiring and Salivating
Pupils unaffected.
Rapidly fed with glucose.
Quick recovery
mms of Hg.
120
110
100
90
80
70
60
50
40
30
20
10
0
7.30am
8
8.30
9
9.30
10
10.30
11
11.30
12.
12.30
Time


Patient E.K. Date 30.1.39. Dose 50 units.
Systolic B.P.
Diastolic B.P.
Early coma.
Deep coma.
Nasally fed with glucose
Quite conscious
Mms. of Hg.
120
110
100
90
80
70
60
50
40
30
20
10
0
7.30
8
8.30
9
9.30
10
10.30
11.
11.30
12.
12.30.
Time.


Patient E.K. Date 2.2.39. Dose 55 units.
Systolic B.P.
Diastolic B.P.
Mms. of Hg.
120
110
100
90
80
70
60
50
40
30
20
10
0
Onset of coma.
Pupils contracted
Deep coma. Salivating and bleeding freely. Warmly fed with glucose.
Quite conscious.
7.30 am
8.
8.30
9.
9.30
10
10.30
11
11.30
12.
12.30
Time.

Patient E.K. Commenced treatment 5.1.39. Left hospital recovered 26.5.39.
Graph showing increase in body weight during Insulin treatment.



CASE 2.

M.D. Single. Aged 16 years. Admitted January 17th, 1939.

Before treatment.

After treatment.

OCCUPATION. Millworker.

HEREDITY. No history of mental illness in ascendants.

PERSONAL HISTORY. The patient was the eldest of a family of five. In early childhood she had measles and chickenpox. She did well at school but did not make many friends. She left school at age of 14 years and commenced work in a cotton mill, her wages were 10/- per week; she had three jobs in three different mills before she broke down in health. In January 1938 the patient's mother died following a confinement, the baby lived. At this time the patient was 15 years of age. She had to look after the house as best she could.

PRE-PSYCHOTIC PERSONALITY. The patient's father, an engine driver, described his daughter as shy and very quiet, but industrious and willing. During the period following her mother's death, the patient had "set to" and worked very hard in the house. She had been very fond of her mother and was also very fond of the other children.

HISTORY of PRESENT ILLNESS. She ceased work on January 6th, 1939 and was admitted to the Municipal hospital on January 8th. She said that a voice had told her that both herself and her father were going to die and were going to join her mother; she was unable to do any work and refused to eat. On January 17th she was admitted to Whittingham.

On admission she was thin and pale, there were no signs of organic disease. W.R. was negative and the C.S.F. report was negative. Mentally she was dull and apathetic, lay in bed gazing at the roof and displaying no interest in her surroundings. Flexibilitas Cerea could be demonstrated on her. Occasionally she had outbursts of screaming. Her habits were faulty. She refused to converse and when attended to resisted violently.

The following notes indicated her progress in hospital.

JANUARY 31st, 1939. "There is no change in her mental state, she lies in bed apathetic and disinterested, will not speak and gazes past me into space. She has to be spoonfed at all meals."

FEBRUARY 14th, 1939. "She is still self-absorbed, has shown little attempt to arouse herself since admission. She will not converse but smiles and mutters to herself appearing hallucinated. Although she was taken to the Occupational Centre she displayed no interest."

FEBRUARY 28th, 1939. "She is still hallucinated and refuses to converse."

On March 3rd insulin treatment was commenced with a dose of 15 units at 7.30 a.m., this was increased by five units per day until at 60 units on March 14th she had her first coma - this was a wet coma. This patient reacted to insulin as follows:- she was drowsy and quiet for one and a half to two hours, there then followed a short period of restlessness with myoclonic movements and finally she developed a wet type of coma.

On March 27th her coma dose had been dropped to 50 units. She was drowsy and quiet up to 9.45 a.m. when some

facial/

facial myoclonus was noticed, at 10.10 a.m. the patient had become restless and was perspiring, this restlessness passed off and by 10.35 a.m. coma had begun. During the restless phase her pupils were dilated but at 10.50 a.m. they were contracted. The coma was of the wet type, perspiration was profuse. At 11.15 a.m. the plantar reflexes were extensor, the patient was salivating, she was in deep coma, the pupils were contracted. She was nasally fed with glucose at 11.25 a.m. and by 11.50 a.m. was wide awake, able and willing to converse.

A mental note on March 28th read "There is a marked improvement in this patient's condition. She is willing and amiable, converses readily. She is taking more interest in her surroundings. She says that the only thing she has against the treatment is that she misses her breakfast and has to stay in bed in the mornings.

No complications occurred with this patient, I found that she did not develop any undue sensitivity to insulin and her coma dose was kept at a point varying between 50 and 65 units throughout treatment. Her condition continued to improve, treatment was concluded on May 9th and the patient left hospital on May 26th. In all she had thirty seven comas.

OBSERVATIONS on PUPIL CHANGES DURING HYPOGLYCAEMIA.

(1) 2.3.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	6.5 mms.	
9.35 a.m.	5 mms.	Drowsy.
10.0 a.m.	4 mms.	Onset of coma, perspiring.
10.25 a.m.	3 mms.)	Deep coma, perspiring, salivating, pulse 70.
11.0 a.m.	3 mms.)	
11.40 a.m.	7 mms.	Awake after Nasal feed.

(2) 22.3.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	6 mms.	Drowsy and quiet.
9.50 a.m.	8.5 mms.	Restless, Myoclonus, pupils dilated.
10.10 a.m.	5 mms.	Commencing coma, pupils contracting.
10.45 a.m.	3.0 mms.	Deep coma. Stimulation of patient made the pupils dilate to 8 mms. after a latent period of 1-2 secs., they remained so for 15 secs. and then contracted again.
11.50 a.m.	7 mms.	Awake after nasal feeding.

(3) 23.3.39.

TIME.	SIZE.	OBSERVATIONS.
9.0 a.m.	6 mms.	Drowsy.
9.45 a.m.	8.5 mms.	Restless.
9.50 a.m.	5 mms.	Short quiet interval in the restless phase.
10.0 a.m.	8 mms.	Restlessness with myoclonus.
10.20 a.m.	5 mms.	Commencing coma.
10.50 a.m.	3 mms.	Deep coma, perspiring freely, salivating profusely. Slow pulse 62.
11.40 a.m.	7.5 mms.	Awake after nasal feed.

(4) 25.3.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.5 mms.	
9.0 a.m.	7 mms.	Drowsy and quiet.
9.30 a.m.	8 mms.	Restless.
10.0 a.m.	8 mms.	Restless, myoclonus.
10.30 a.m.	4 mms.	Coma.
11.0 a.m.	3 mms.	Deep coma, perspiring and salivating.
11.45 a.m.	7 mms.	Awake after nasal feeding.

(5) 29.3.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	7 mms.	
9.40 a.m.	7.5 mms.	Restless.

(5) Contd.

TIME.	SIZE.	OBSERVATIONS.
9.55 a.m.	5.5 mms.	Short quiet interval in the restless phase.
10.0 a.m.	8 mms.	Restless, myoclonus.
10.40 a.m.	5 mms.	Coma, perspiring.
11.0 a.m.	3 mms.	Deep coma, perspiring, salivating, stimulation produced a dilatation of the pupil after a latent period of 1-2 secs. At the same time the pulse quickened. When left alone the pupil contracted again and the pulse slowed.
11.40 a.m.	7 mms.	Awake after nasal feeding.

(6) 30.3.39.

TIME.	SIZE.	OBSERVATIONS.
9.20 a.m.	7 mms.	Drowsy.
10.0 a.m.	8 mms.	Restlessness. Myoclonus. Pupils dilated.
10.30 a.m.	3 mms.	
11.0 a.m.	3 mms.	Deep coma, perspiring, salivating. Slow pulse 60.
11.35 a.m.	6.5 mms.	Awake after nasal feeding.

(7) 3.4.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.15 a.m.	7 mms.	Drowsy.
10.0 a.m.	7.5 mms.	Restlessness.
10.4 a.m.	6 mms.	Quiet interval in the restless phase.
10.15 a.m.	8 mms.	Restlessness, pupils dilated.
10.30 a.m.	6 mms.	
10.55 a.m.	3.5 mms.	
11.25 a.m.	3 mms.	Deep coma.
12.0 a.m.	6.5 mms.	Awake after nasal feeding.

(8) 4.4.39.

TIME.	SIZE.	OBSERVATIONS.
9.0 a.m.	7 mms.	Drowsy.
9.45 a.m.	8 mms.	Restless.
9.51 a.m.	5.5 mms.	Quiet interval in restless phase.
10.10 a.m.	8 mms.	Restlessness, Myoclonus.
10.45 a.m.	3.5 mms.	
11.15 a.m.	3 mms.	Deep coma.
11.45 a.m.	7 mms.	Awake after nasal feeding.

(9) 5.4.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.5 mms.	
9.0 a.m.	7 mms.	
9.50 a.m.	8 mms.	Restlessness.
10.15 a.m.	8 mms.	"
10.45 a.m.	3 mms.	
11.20 a.m.	3 mms.	Deep coma, perspiring, salivating.
11.55 a.m.	7 mms.	Awake after nasal feeding.

(10) 6.4.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	7 mms.	Drowsy.
9.35 a.m.	8 mms.	Restless.
9.42 a.m.	6 mms.	Quiet interval during the restless period.
10.0 a.m.	8 mms.	Restlessness.
10.30 a.m.	3 mms.	Deep coma, perspiring, salivating.
11.0 a.m.	3 mms.	Slow pulse 58.
11.50 a.m.	7 mms.	Awake after nasal feeding.

(11) 8.4.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.5 mms.	
9.0 a.m.	7 mms.	
9.15 a.m.	7 mms.	Drowsy and quiet.
9.45 a.m.	8 mms.	Restless.
10.10 a.m.	4 mms.	Early coma, perspiring.
10.30 a.m.	3 mms.	Deep coma, perspiring and salivating. Slight stimulation of the patient made the pupils dilate to 8 mms. after a latent period of 1-2 secs. at same time pulse rate quickened. When left alone the pupils contracted again and the pulse slowed.
11.0 a.m.	3 mms.	
11.55 a.m.	7 mms.	Awake after nasal feeding.

(12) 12.4.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.5 mms.	
9.5 a.m.	6 mms.	
9.40 a.m.	7.5 mms.	Becoming restless.
9.52 a.m.	5.5 mms.	Quiet interval.
10.0 a.m.	8 mms.	Very restless. Perspiring.
10.30 a.m.	4 mms.	
11.0 a.m.	3 mms.	Deep coma, perspiring, salivating. Slow pulse 62.
12.0 noon	7 mms.	Awake after nasal feeding.

In this patient the procession of events after injection was firstly a drowsy quiet period of 1½ - 2 hours during which the tendency was for the pupils to contract; following this period was a restless phase with myoclonus, during this phase the pupils were widely dilated but it was noticed if a short quiet interval intervened in the restless period, the pupils became smaller. With the onset of coma, the pupils became definitely contracted, but at the same time would dilate, on stimulation, after a latent period of 1 - 2 secs. After a period of 10-25 secs. the pupils contracted again and remained so if the patient was left quiet.

BLOOD SUGAR OBSERVATIONS.

A blood sugar tolerance test and three blood sugar curves following insulin are shown. Points were :-

(1) The greatest fall in the blood sugar occurred in the first one and a half to two hours that was when apart from drowsiness there were no symptoms.

(2) In one of the graphs following a bout of restlessness with myoclonus there was a rise in the blood sugar; at this point coma was commencing. As coma developed the blood sugar fell even further.

(3) After the nasal feed, the patient was quite conscious/

conscious and yet the blood sugar level was not as high as the fasting level at which she started the morning.

PULSE RATE OBSERVATIONS.

Pulse rates were taken every day at half hourly intervals between 7.30 a.m. and 1.30 p.m., nine charts of this particular patient are shown. The initial tachycardia was noticed and concurrent with this was the restless myoclonic period. This was followed by a deepening coma and a slowing of the pulse. On the chart for 2.5.39, myoclonus supervened during coma and brought about an acceleration of the pulse from seventy to a hundred and ten. Simple stimulation of the patient during the coma period produced a momentary quickening of the pulse which quickly slowed again when the patient was left quiet.

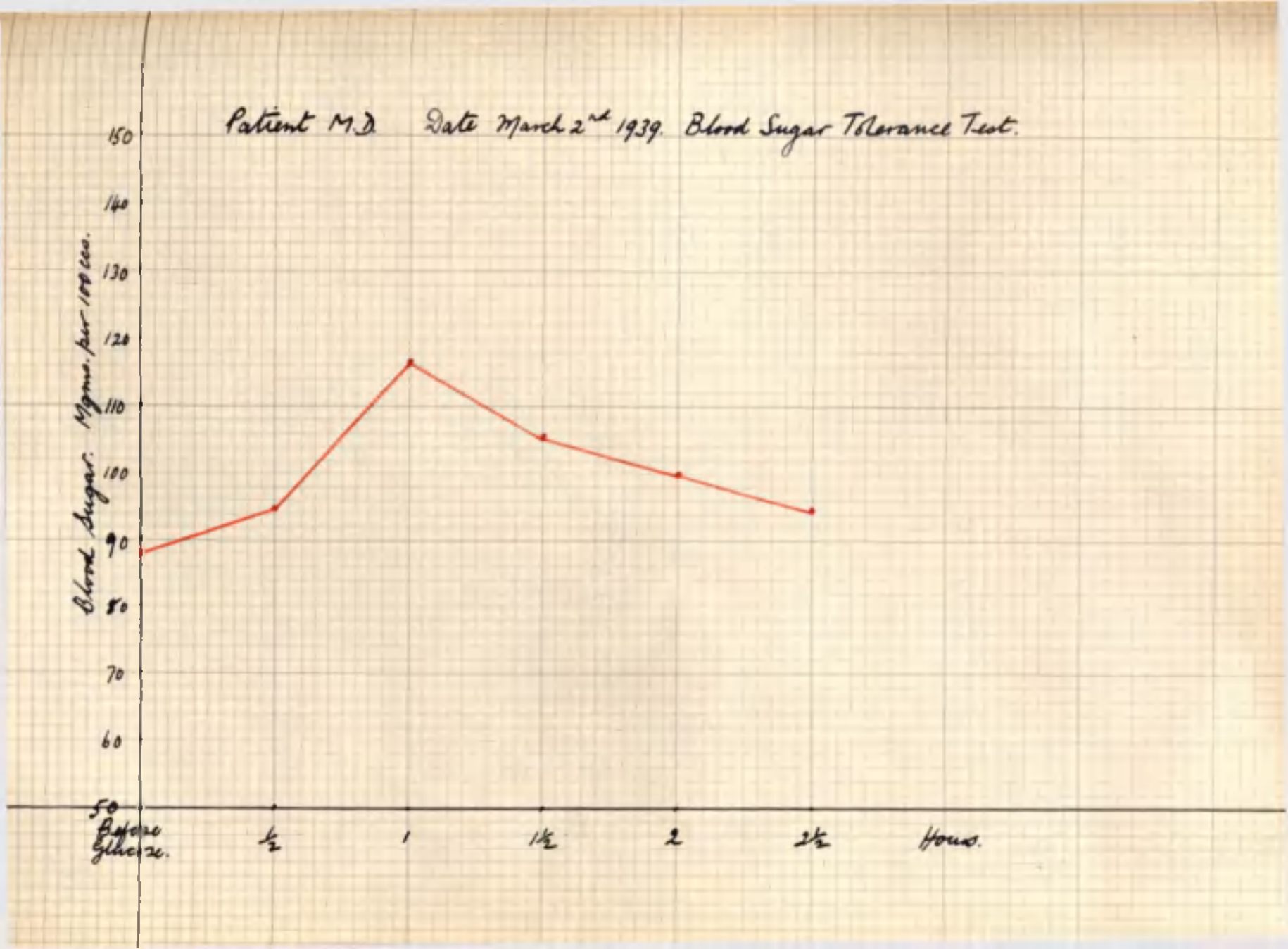
BLOOD PRESSURE OBSERVATIONS.

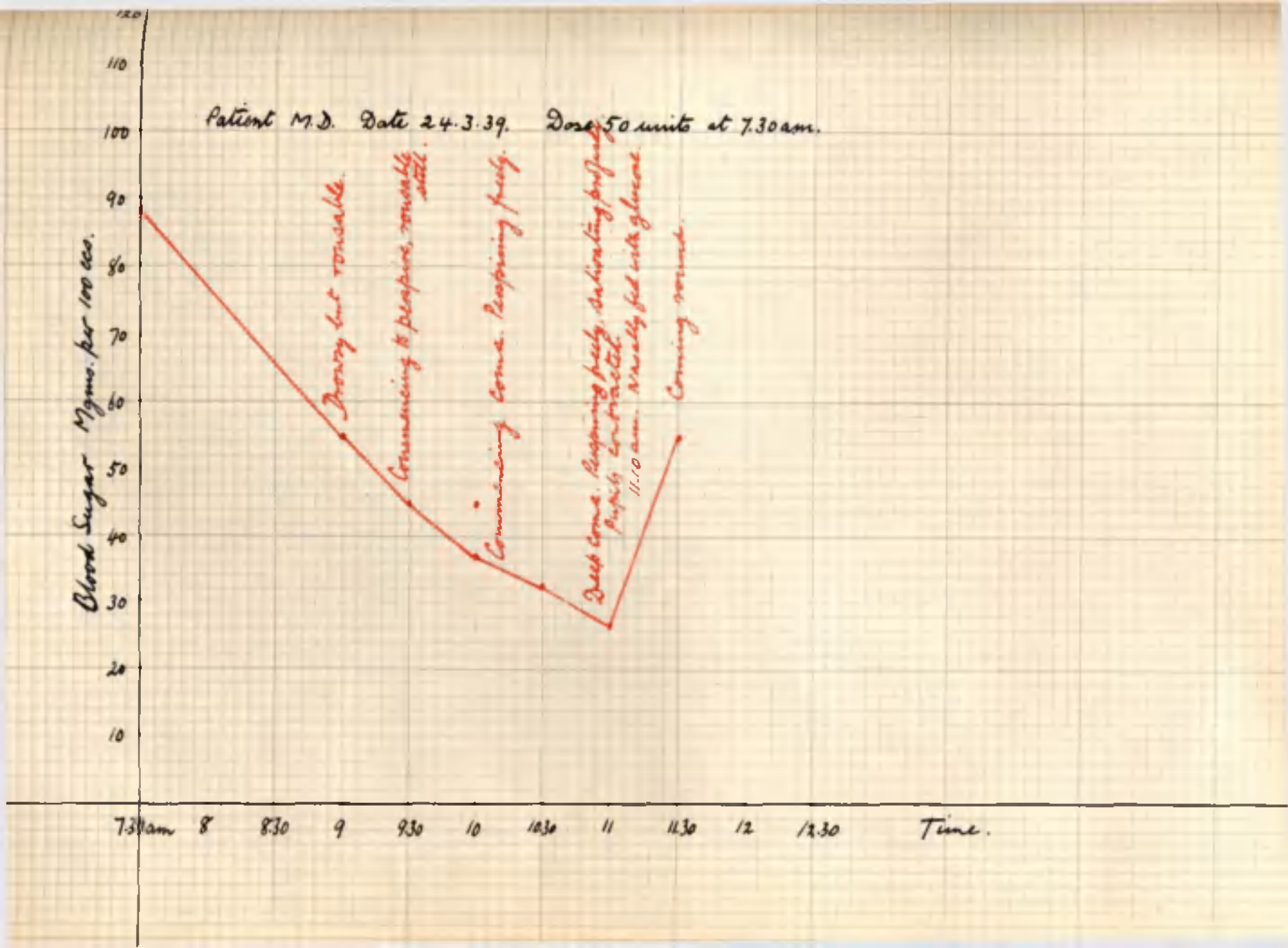
In this patient in the early stages corresponding to the restless myoclonic phase there was a rise in both systolic and diastolic pressures, a greater rise occurred in the systolic than in the diastolic. As coma developed both systolic and diastolic pressures fell below normal, a

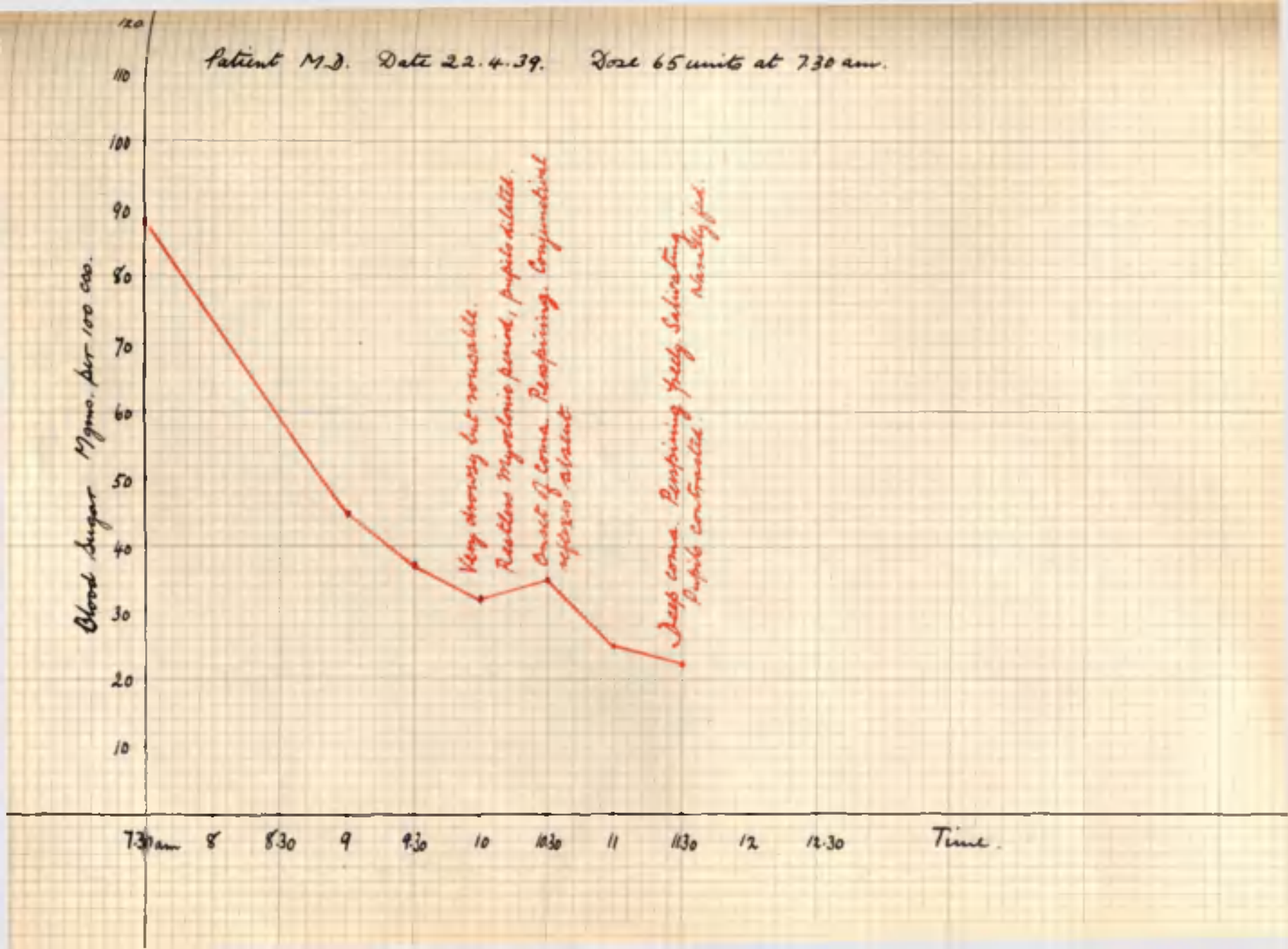
greater/

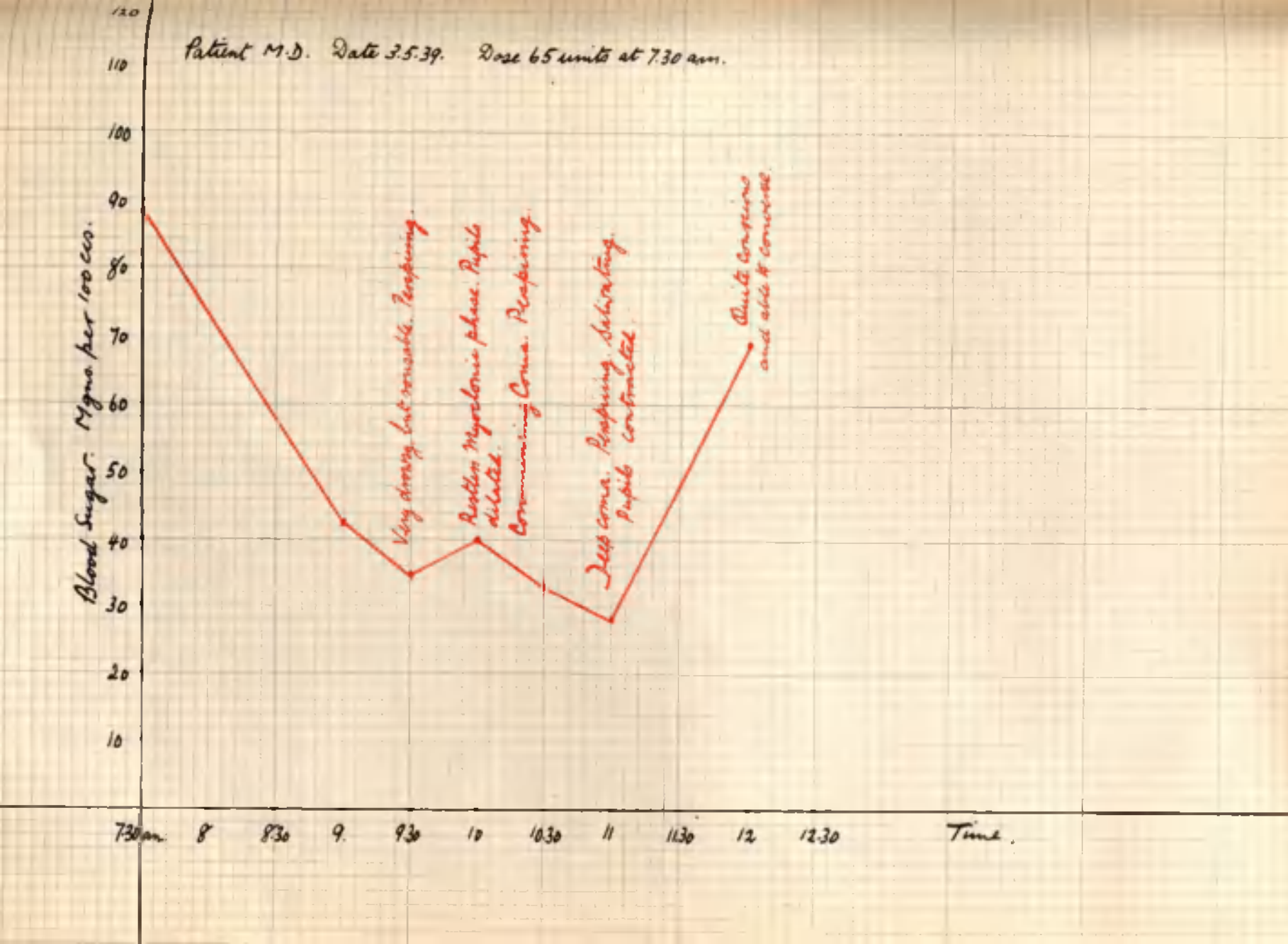
greater fall occurred in the diastolic than in the systolic, the pulse pressure was thus increased. After nasal feeding when the patient was awake, both pressures had moved towards normal.

The weekly graph of weight in this patient showed a definite upward curve.


Patient M.D. Date March 2nd 1939. Blood Sugar Tolerance Test.
Blood Sugar. Mgms. per 100 ccs.
150
140
130
120
110
100
90
80
70
60
50
Before Glucose.
½
1
1½
2
2½
Hours.


Patient M.D. Date 24.3.39. Dose 50 units at 7.30 am.
Blood Sugar Mgms. per 100 cc.
120
110
100
90
80
70
60
50
40
30
20
10
Beauty but restless.
Commencing to perspire, restless still.
Commencing coma. Perspiring freely.
Deep coma. Respiring freely, salivating profusely. Pupils contracted.
11.10 am. Nearly fed with glucose.
Coming round.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.


Patient M.J. Date 22.4.39. Dose 65 units at 7.30 am.
Blood Sugar Mgms. per 100 cc.
120
110
100
90
80
70
60
50
40
30
20
10
Very sweaty but rousable.
Reaction Hypoglycaemic Pupils dilated.
Coma. Respiring. Conjunctival reflex present
Deep coma. Respiring freely. Salivating. Pupils contracted. Nausea. Vomiting.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.


Patient M.D. Date 3.5.39. Dose 65 units at 7.30 am.
Blood Sugar Mgms per 100 cc.
120
110
100
90
80
70
60
50
40
30
20
10
Very strong but remarks. Perspiring.
Restless Myoclonic phase. Pupils dilated.
Commencing Coma. Perspiring.
Deep Coma. Perspiring. Salivating. Pupils contracted.
Quite conscious and able to converse.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.

4 HOUR CHART

DISEASE

M.D.

Name

Age

Diet

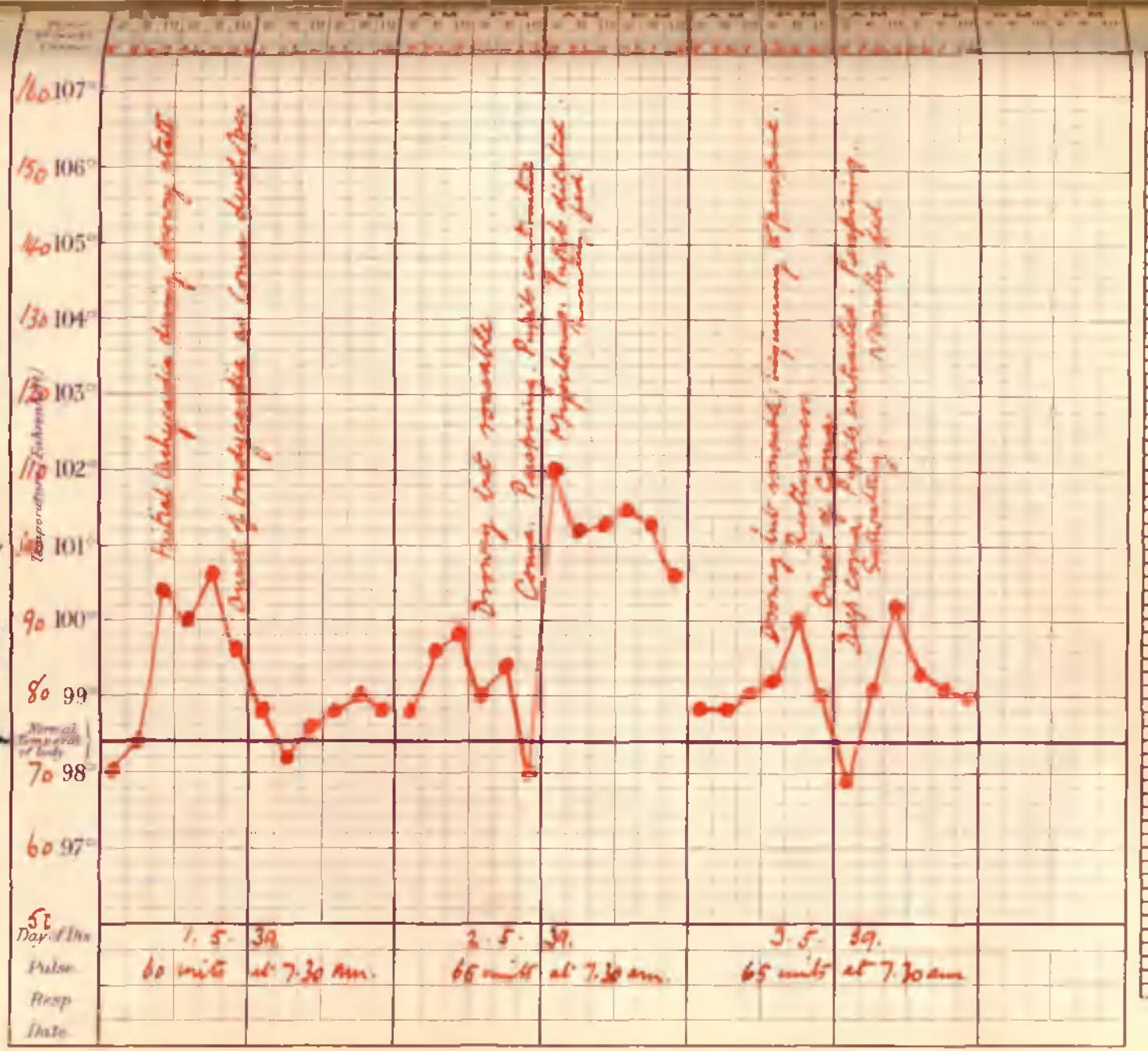
Case Book N°

Notes of Case

Three pulse records.
① Straightforward initial tachycardia followed by bradycardia as coma developed.
② Myoclonus occurring during coma raised the pulse rate.
③ Initial tachycardia followed by bradycardia.

Date of admission

Result



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4 HOUR CHART.

DISEASE.

Name { M.D.

Age

Diet

Case Book No.

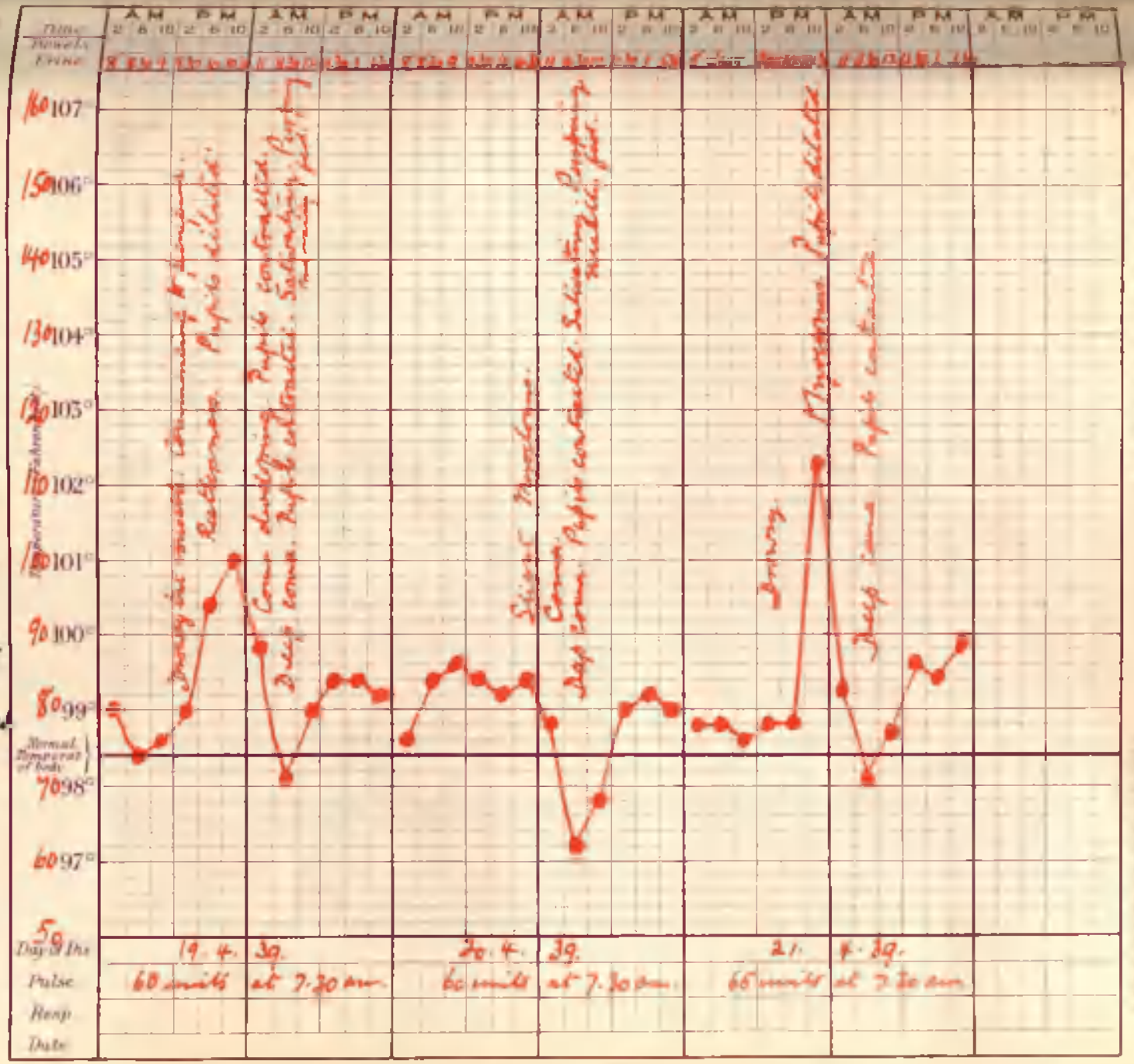
Notes of Case

The first two pulse records show the initial tachycardia followed by bradycardia as Coma developed.

The third record showed the effect of a bout of myoclonus on the pulse; it quickened and later slowed down.

Date of admission

Result



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4 HOUR CHART.

DISEASE

Name M.D.

Age

Diet

Case Book No.

Notes of Case

Three pulse records of the same patient.

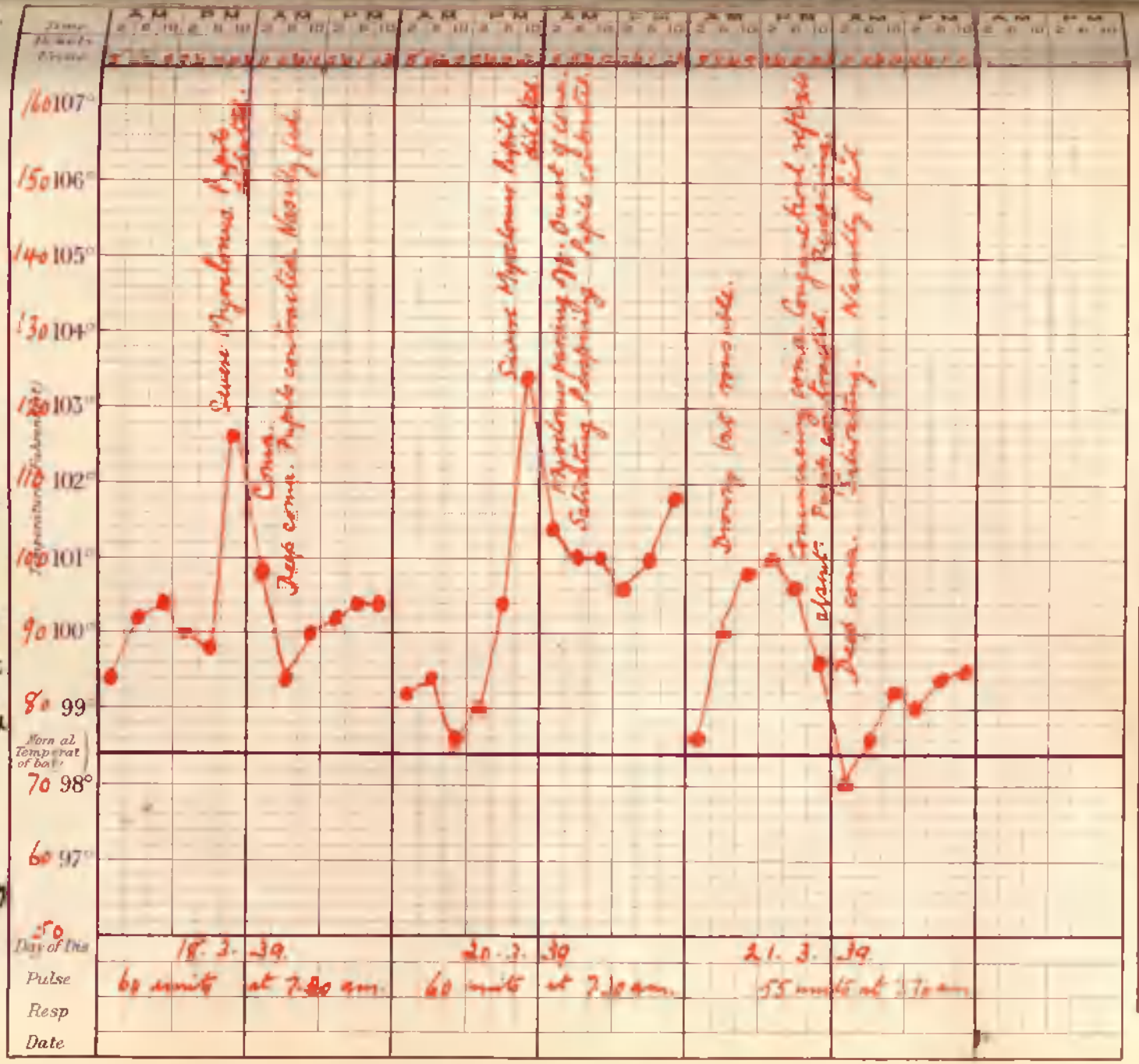
① Initial tachycardia followed by some slowing which was interrupted by a bout of myoclonus which accelerated the pulse rate. When coma did set in, the bradycardia developed again.

② Similar to ①.

③ A smaller dose produced the initial tachycardia, followed by the bradycardia and not interrupted by any myoclonus.

Date of admission

Result



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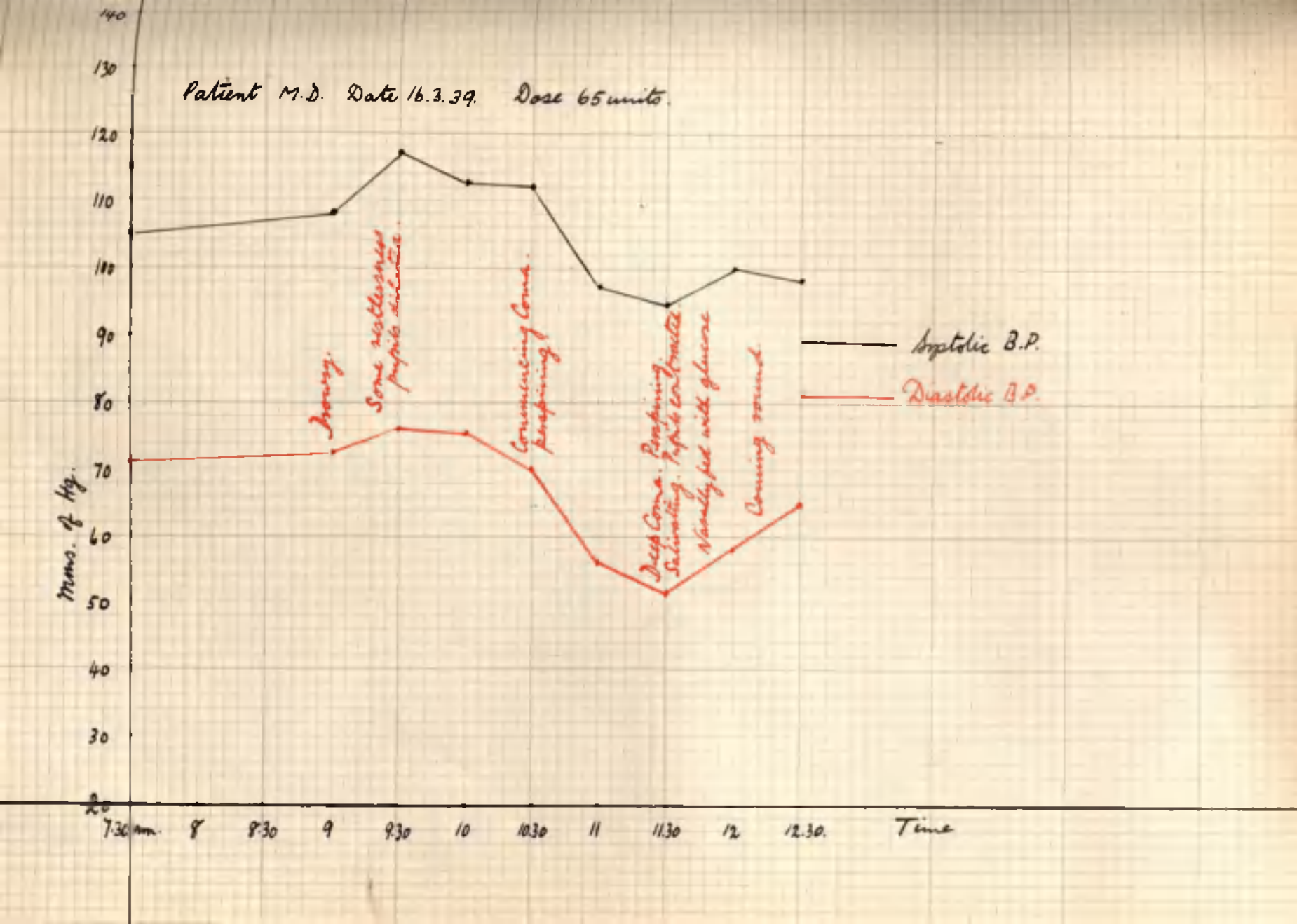
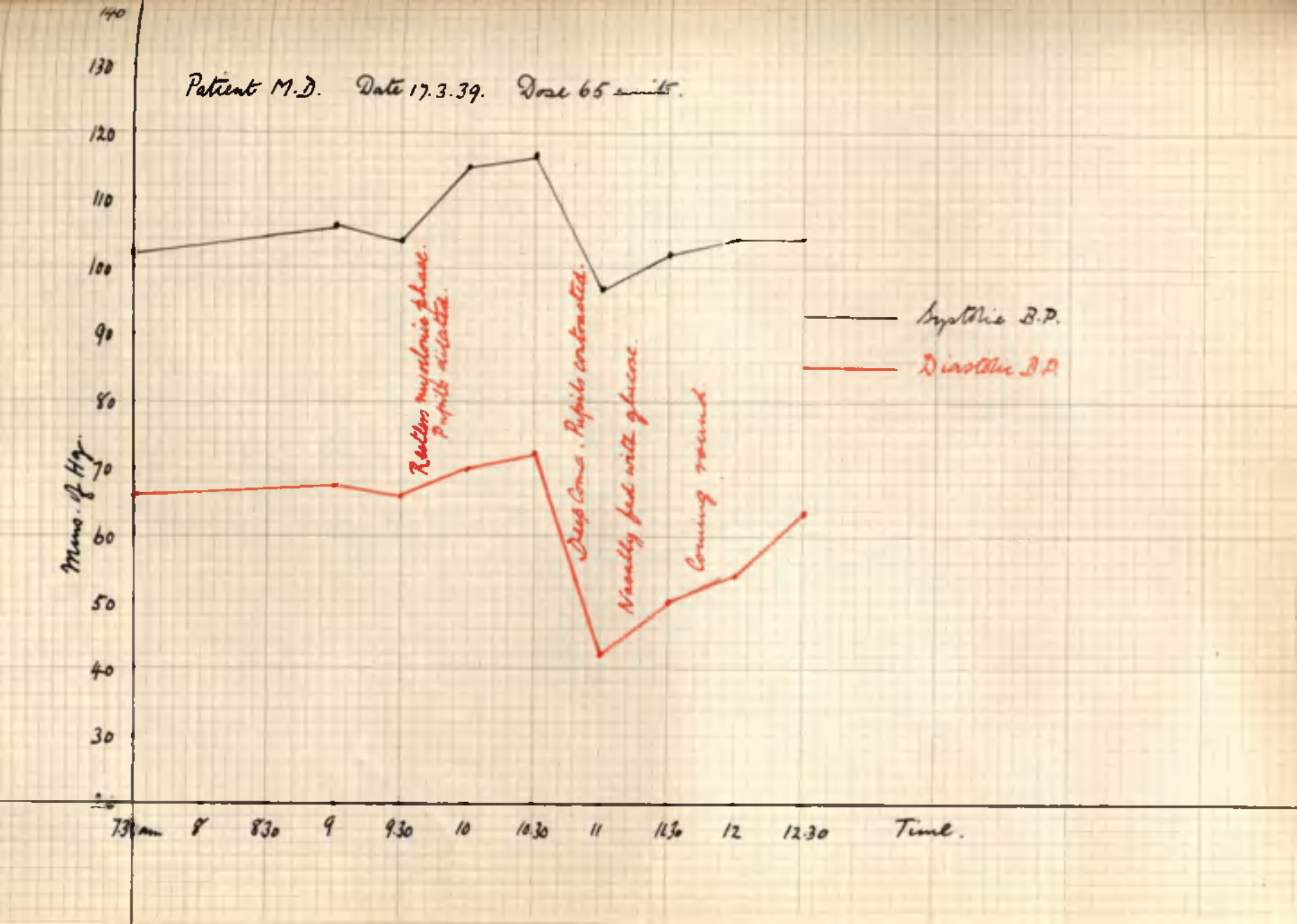
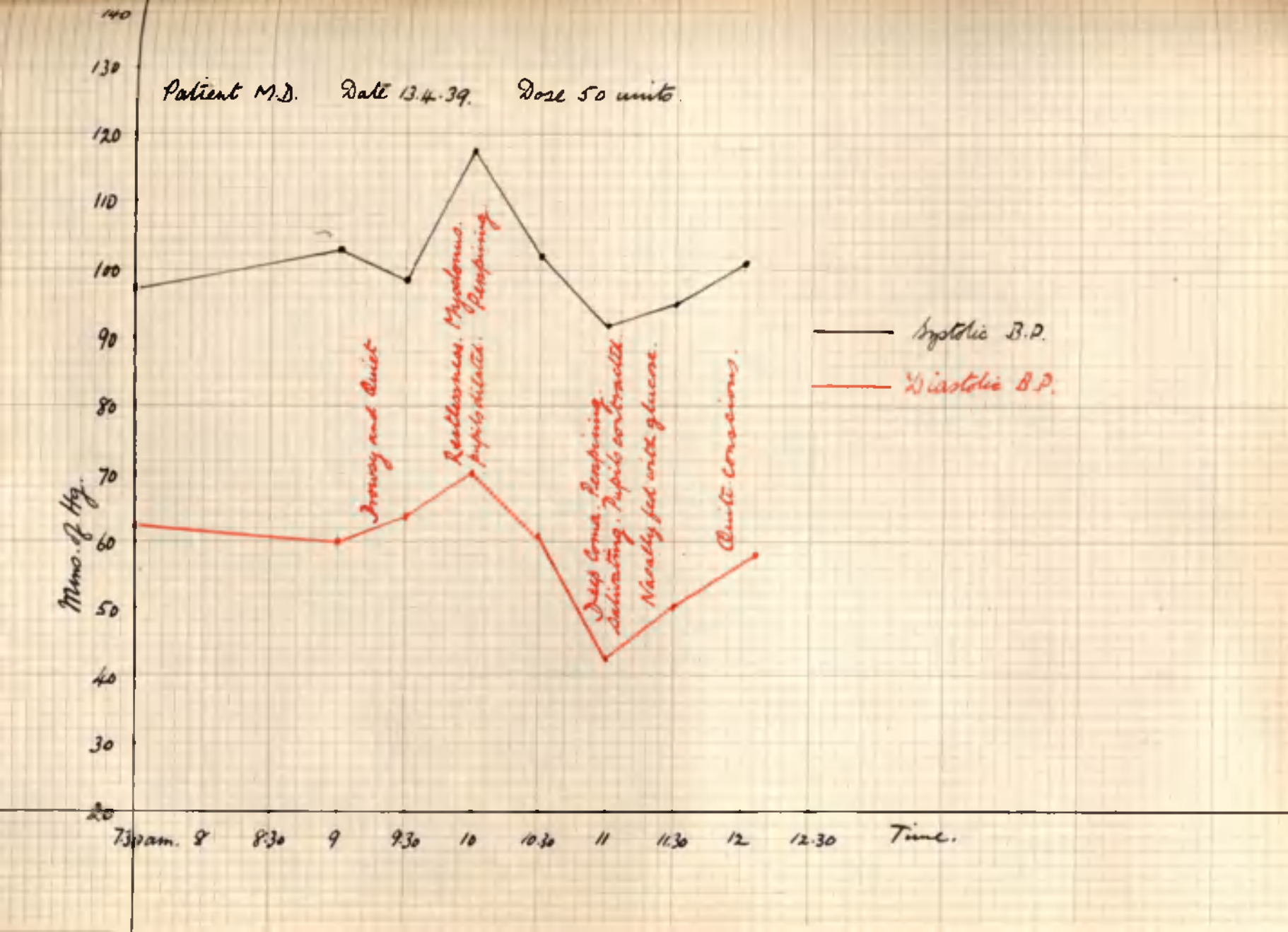
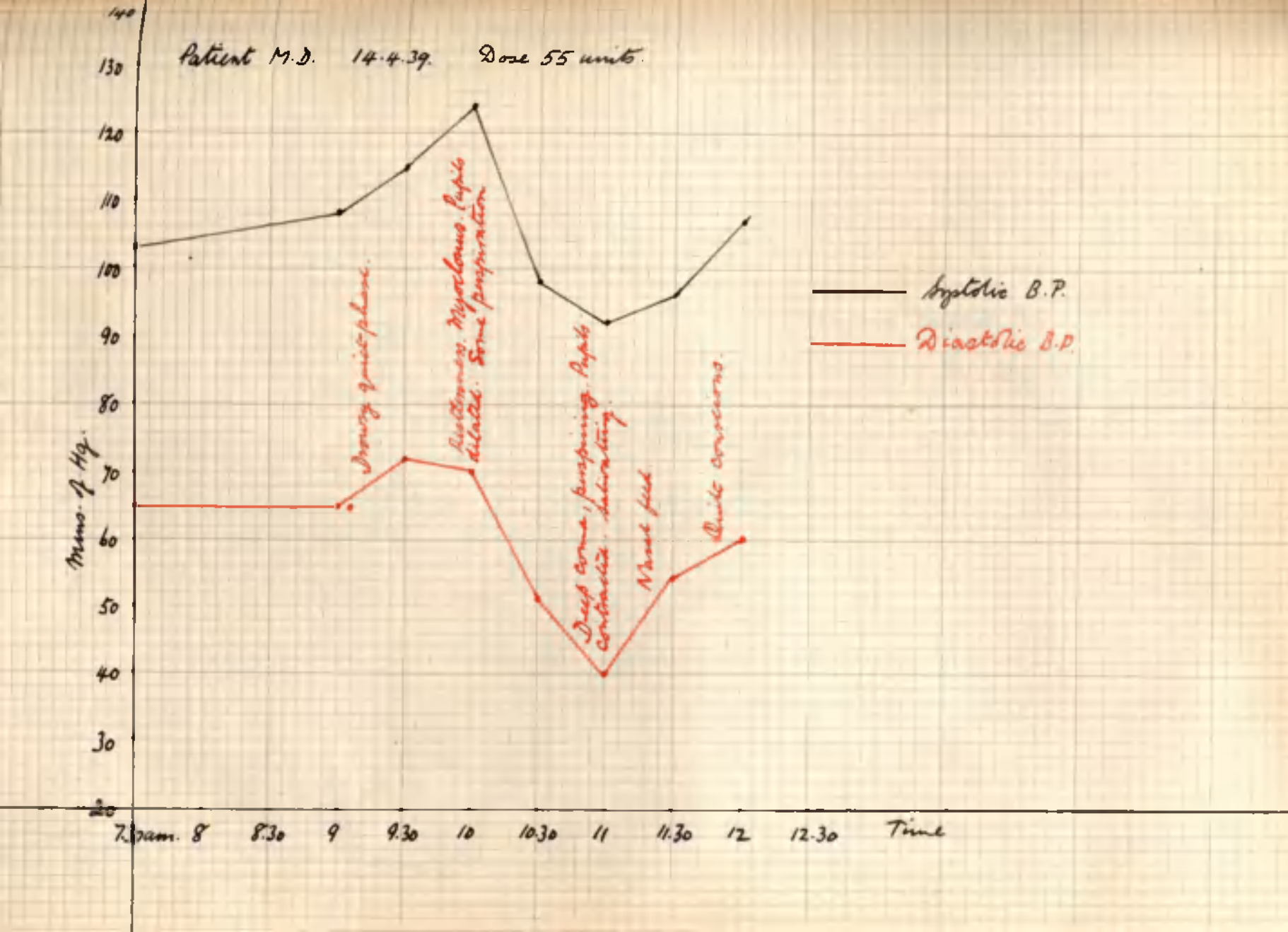
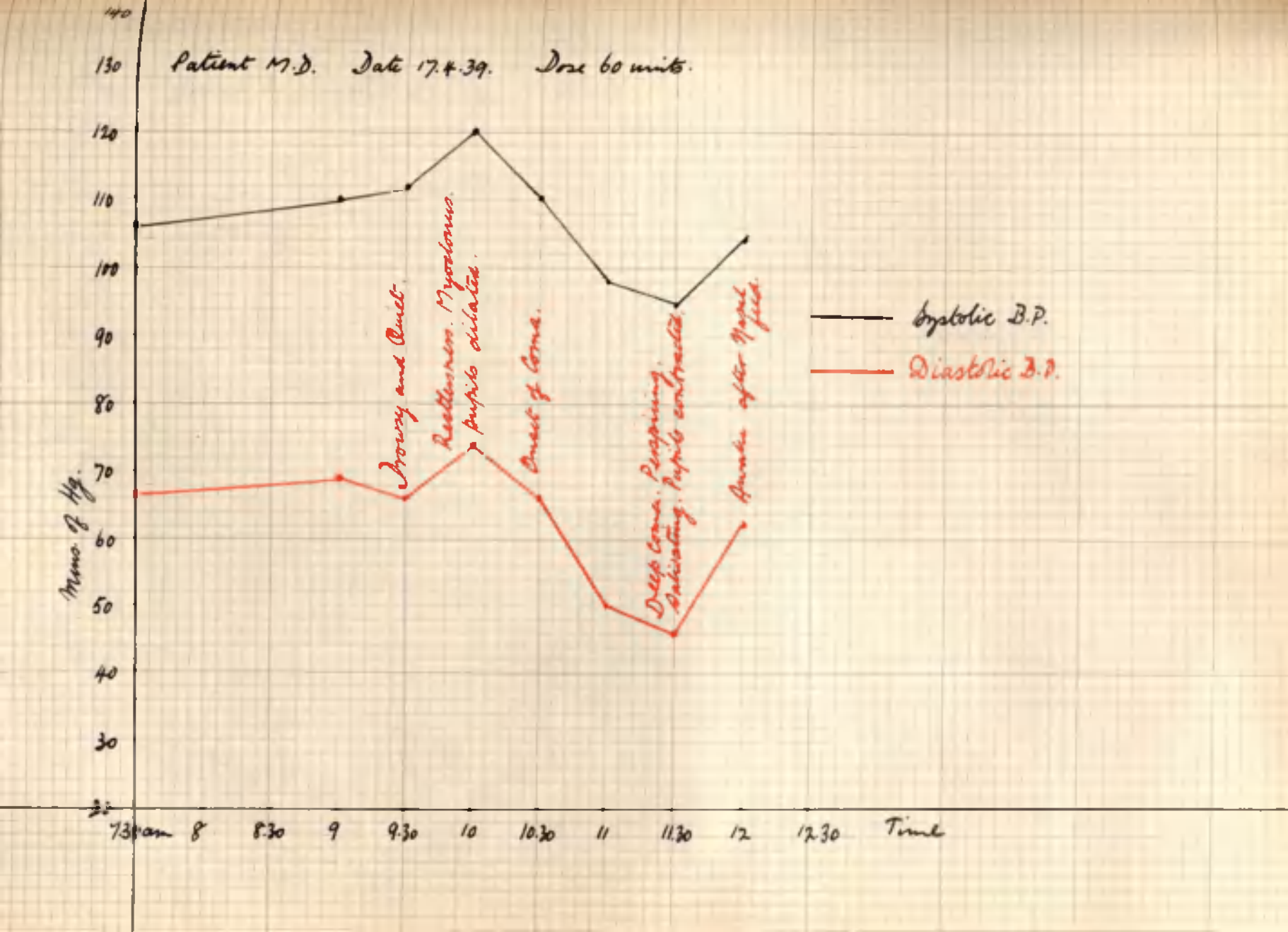
Goulds Clinical Chart

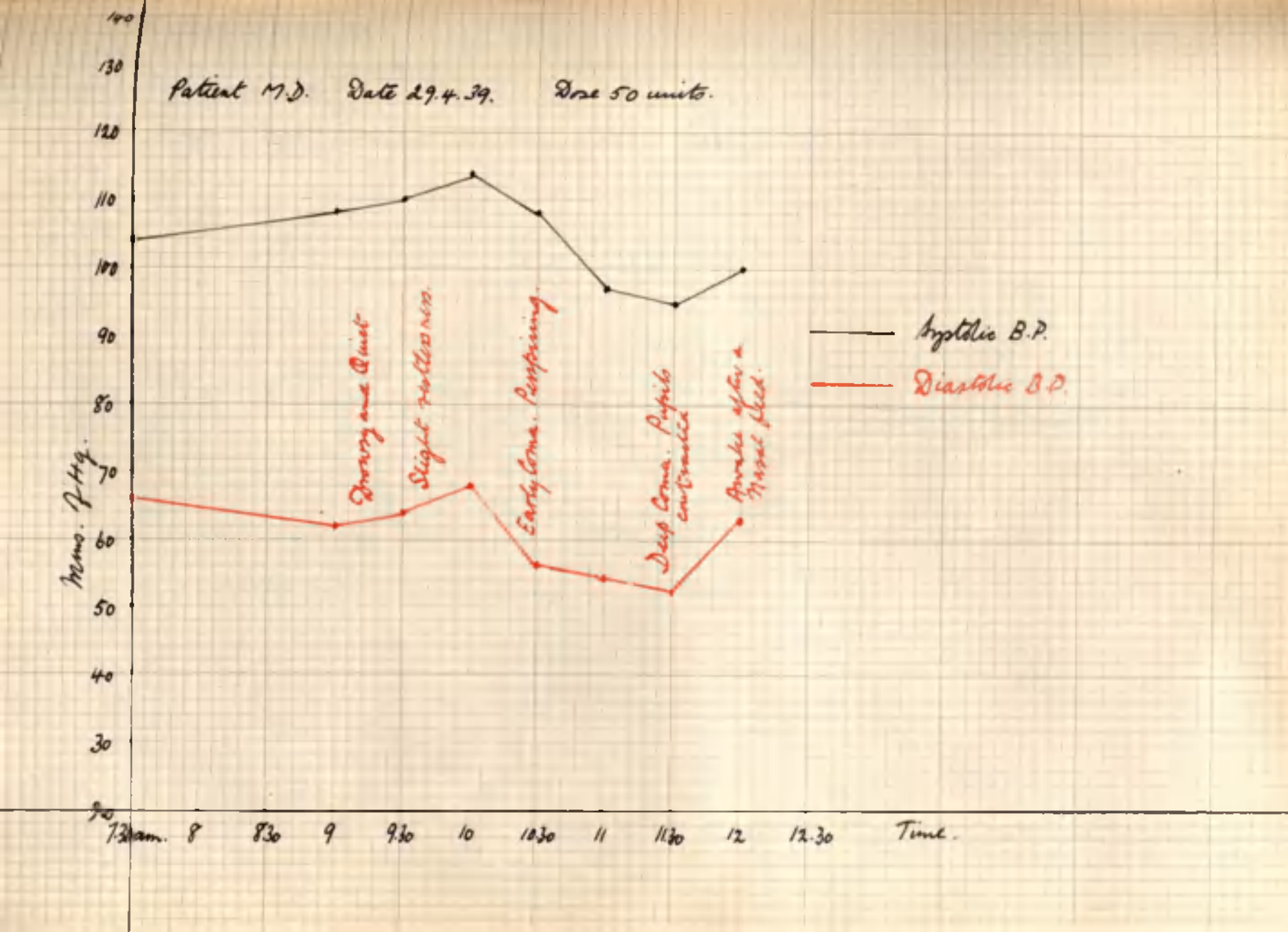

Patient M.D. Date 16.3.39. Dose 65 units.
mms. of Hg.
140
130
120
110
100
90
80
70
60
50
40
30
20
7.30 am.
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30.
Time
Systolic B.P.
Diastolic B.P.
Drowsy.
Some restlessness
Profuse sweating.
Commencing Coma.
Deep Coma. Perspiring.
Salivating. Pupils contracted.
Vomiting.
Handling face with gloves
Coming round


Patient M.D. Date 17.3.39. Dose 65 units.
140
130
120
110
100
90
80
70
60
50
40
30
Mms. of Hg.
Restless, mydriasis, flush. Pupils dilated.
Blue Cons. Pupils contracted.
Vomiting, faint with glucose.
Coming round.
Systolic B.P.
Diastolic B.P.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.

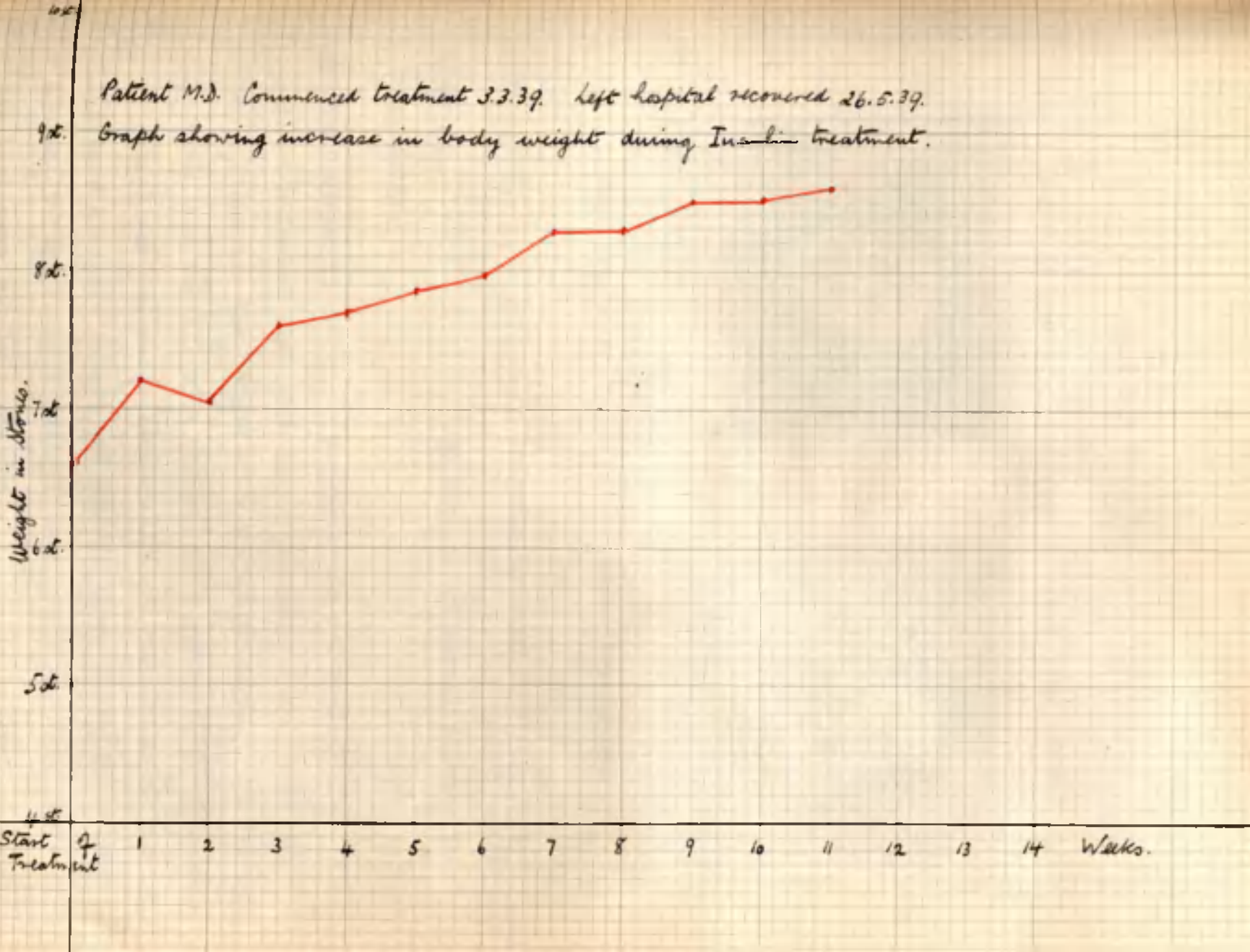

Patient M.D. Date 13.4.39. Dose 50 units.
Mms. of Hg.
140
130
120
110
100
90
80
70
60
50
40
30
20
7.30 am. 8 8.30 9 9.30 10 10.30 11 11.30 12 12.30 Time.
Drowsy and quiet
Restlessness. Hyperpnoea. Pupils dilated. Perspiring.
Deep coma. Perspiring. Salivating. Pupils contracted.
Scarcely felt with glucose.
Quite conscious.
Systolic B.P.
Diastolic B.P.


Patient M.D. 14.4.39. Dose 55 units.
Systolic B.P.
Diastolic B.P.
Mms. of Hg.
140
130
120
110
100
90
80
70
60
50
40
30
20
7 am.
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time
Drowsy, pricks of sweat.
Restlessness, Myoclonus, Pupils dilated. Some perspiration
Deep coma; perspiring. Pupils contracted. Salivating.
Mouth foul.
Quite conscious.


Patient M.D. Date 17.4.39. Dose 60 units.
Mms of Hg.
140
130
120
110
100
90
80
70
60
50
40
30
Drowsy and Quiet.
Restlessness. Myoclonus. Pupils dilated.
Coma of Coma.
Deep Coma. Perspiring. Salivating. Pupils contracted.
Awoke after 9 hours fast.
Systolic B.P.
Diastolic B.P.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time


Patient M.D. Date 29.4.39. Dose 50 units.
140
130
120
110
100
90
80
70
60
50
40
30
20
Mms. Hg.
Drowsy and Quiet
Slight Twitchings.
Early Coma. Perspiring.
Deep Coma. Pupils contracted
Awoke after 2 Normal Meal.
Systolic B.P.
Diastolic B.P.
7.30 am. 8 8.30 9 9.30 10 10.30 11 11.30 12 12.30 Time.

Patient M.D. Commenced treatment 3.3.39. Left hospital recovered 26.5.39.
Graph showing increase in body weight during Insulin treatment.



C A S E 3.

D.L. Aged 25 years. Admitted October 13th, 1938.

Before treatment.

After treatment.

OCCUPATION. Domestic servant.

HEREDITY. No history of mental illness in ascendants.

PERSONAL HISTORY. Mother alive and well. The patient's father died from lobar pneumonia five years ago. The patient was the eldest of a family of three. At the age of seven she was ill with chorea, this lasted three months. At school she did well, reached the top standard; at age of fourteen she left school and for the next eleven years she worked at home or as a domestic servant in her home town. Her best wage was 15/- per week.

PRE-PSYCHOTIC PERSONALITY. Her mother and sister who visited the patient in hospital described her as a daydreaming type of girl, given to enthusiasms which lasted only a short time. They said she was "mad" on the cinema. She was easy to get on with and always willing.

HISTORY of PRESENT ILLNESS. In the early months of 1938 the patient began to be very interested in religion, she and a girl friend used to spend many evenings together reading the Bible and discussing how they could make better Christians of themselves. In September 1938 during the war scare it came to the patient's knowledge that her friend was going out with a young man; she immediately went to her friend's house, an angry emotional scene occurred, she accused her friend of deserting her and their Christian ideals. When the patient got home she had what appeared to be a violent hysterical attack and then said that her father was alive although he had been dead some time. Her conduct thereafter was very strange, she was violent at times and threatened her mother and sister. She was taken to the municipal hospital on October 11th and was admitted to Whittingham on October 13th.

On admission her physical condition was good, there were no signs of organic disease, but bruises were noticed

on/

on all parts of her body. W.R. was negative, C.S.F. report was negative. Mentally she was restless, excited and difficult with her food. She appeared to be confused and all she would say was "I have broken her heart".

The following notes indicated her progress in hospital.

NOVEMBER 3rd, 1938. "She appears to be suffering from Dementia Praecox, she is constantly laughing and grimacing in a foolish manner. She is untidy, her habits are faulty and she is extremely mischievous. e.g. she delights in pulling the petals off the ward flowers."

DECEMBER 16th, 1938. "Her manner and conversation are still foolish; she has no insight into her condition, when allowed up she wanders about the ward interfering generally in a mischievous manner."

Insulin treatment was commenced on January 4th 1939 with a dose of 15 units, this was increased by five units daily until on January 19th with a dose of 70 units she had her first coma. Light coma commenced at 11.20 a.m. following a very restless period from 10.50 a.m. to 11.15 a.m. during which the patient was perspiring freely and salivating, her pupils were widely dilated. Prior to the restless period the patient had been very quiet. Glucose was given at 11.50 a.m.

and/

and the patient was awake at 12.5 p.m.

Treatment was continued daily and it became obvious that this patient reacted to insulin in a very definite manner. She was drowsy and quiet from 7.30 a.m., the time of injection, until a time varying from 10 a.m. to 10.45 a.m., then there followed a period of very great restlessness with myoclonus, the patient rolled about the floor of the sideroom in which she had to be placed; this was accompanied by free perspiration and salivation and during the whole of this time the pupils were widely dilated but unmeasurable owing to the patient's restlessness. I thought that this restless period was the prelude to a fit so I never allowed it to continue very long, the longest period being about forty five minutes. On one occasion this patient did have a fit following a period of restlessness. The patient, although not in a state of deep coma, was seldom able to drink the glucose and therefore had to be nasally fed. At odd times usually on a Monday morning after the Sunday rest from treatment, I found that the restless period brought this patient round sufficiently for her to drink her glucose. The complication of vomiting occurred in this patient but was successfully dealt with by the addition of a tablespoonful of bismuth mixture to the glucose and by very thorough aspiration of the stomach

contents/

contents prior to feeding although this was generally very difficult in this struggling restless patient. As this patient began to improve mentally very soon after the commencement of treatment, no attempt was made to change her type of reaction to insulin.

On January 11th a mental note read "There is no material change in this patient's mental condition, she wanders about the ward interfering in a mischievous manner with the other patients and with the staff, is often seen grinning and grimacing to herself in a foolish manner.

On February 9th she had 45 units at 7.30 a.m., the patient remained very quiet and drowsy until 10.45 a.m. when she began to be slightly restless, this restlessness increased until by 11.10 a.m. the patient was rolling about the sideroom floor, her arms and legs were moving spasmodically and her face was twitching, she was perspiring freely. Her pupils could not be measured but they could be seen to be widely dilated. At 11.35 a.m. she was still as restless as ever and was nasally fed with glucose and a tablespoonful of bismuth mixture, by 12 noon she was quite conscious and able to converse. A mental note made during that afternoon said "During the past month, this patient has improved in her

mental/

mental state, she is more stable now, pleasant in manner and willing to occupy herself usefully; she has ceased wandering about the ward in an aimless silly manner. She realises she has been ill and is eager to get better and go home.

Treatment was stopped on March 13th. In all she had twenty eight light comas; although the nasal feeding of this patient was always a struggle, she had no recollection of this struggle and when she finished treatment she said that she was glad she had had the treatment because it had made her well again. She left hospital recovered on March 27th.

PUPIL OBSERVATIONS.

It was found impossible to make any series of measurements of the pupils in this patient. She became so restless that she was always in a side room on the floor during the whole of treatment. Although it was impossible to measure her pupils during the restless phase, it was easily seen that they were widely dilated and remained so until after nasal feeding.

BLOOD SUGAR OBSERVATIONS.

It was not always possible to obtain the blood in this patient owing to her restlessness. A blood sugar tolerance

graph/

graph and three blood sugar graphs after insulin are shown. The blood sugar tolerance test was normal. In this patient there was not such a great fall as seen in other patients but the same rapid steep fall occurred in the first one and a half to two hours. During the restless period there was a definite rise in the blood sugar. As usual the patient could be quite conscious and able to converse and yet the blood sugar level was far from being as high as it was at the beginning of the morning's treatment.

PULSE RATE OBSERVATIONS.

Nine of the daily charts are shown, in all it was noticed that there was a marked increase in the rate of the pulse and this occurred with the onset and during the restless myoclonic phase. In addition there was a dilatation of the pupil, free perspiration and increased salivation. Following the nasal feed with glucose there was a slowing of the pulse. This occurred regularly every morning.

BLOOD PRESSURE OBSERVATIONS.

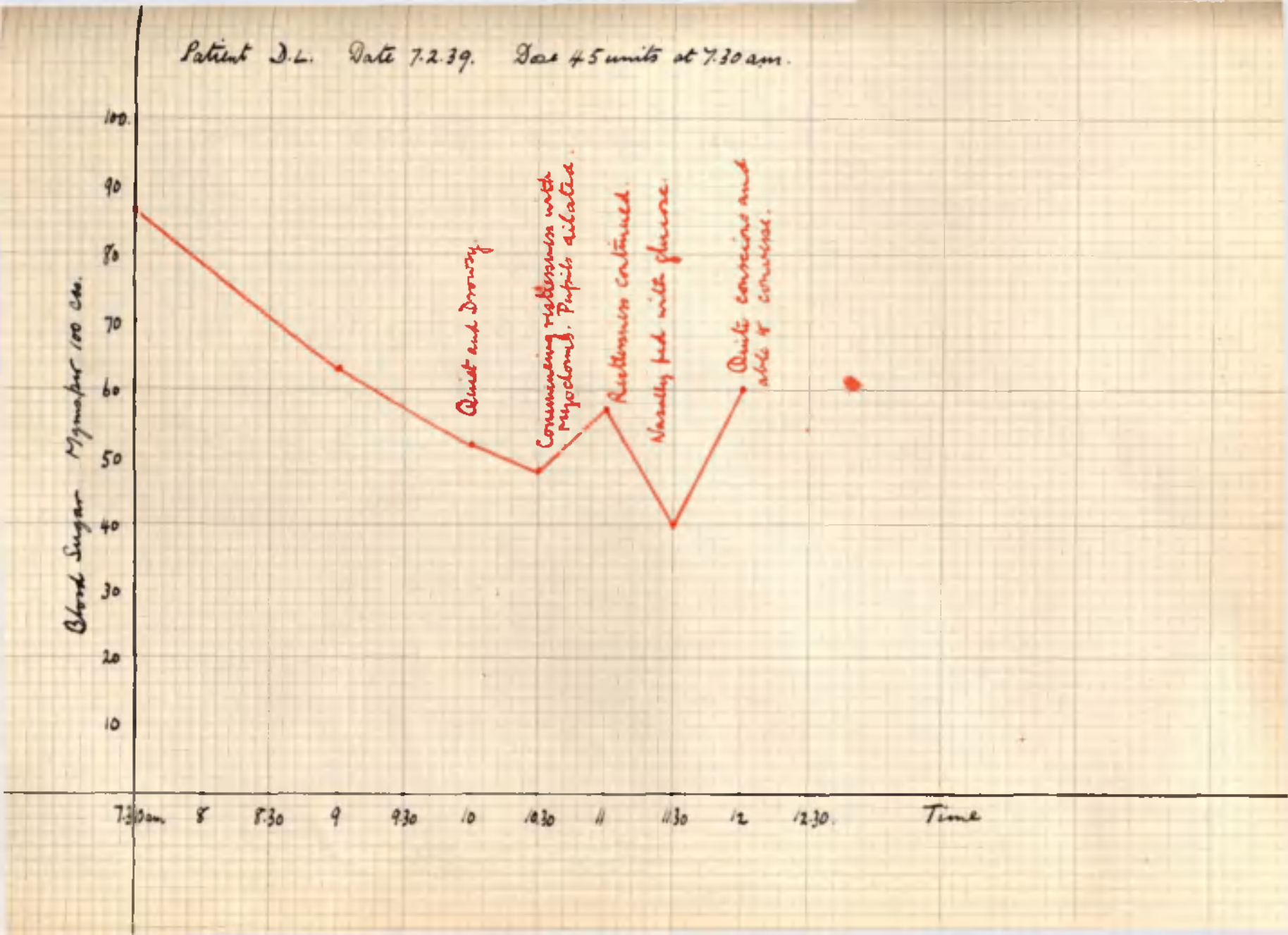
It was impossible to take the blood pressure during the restless phase. Three attempts at graphing the blood

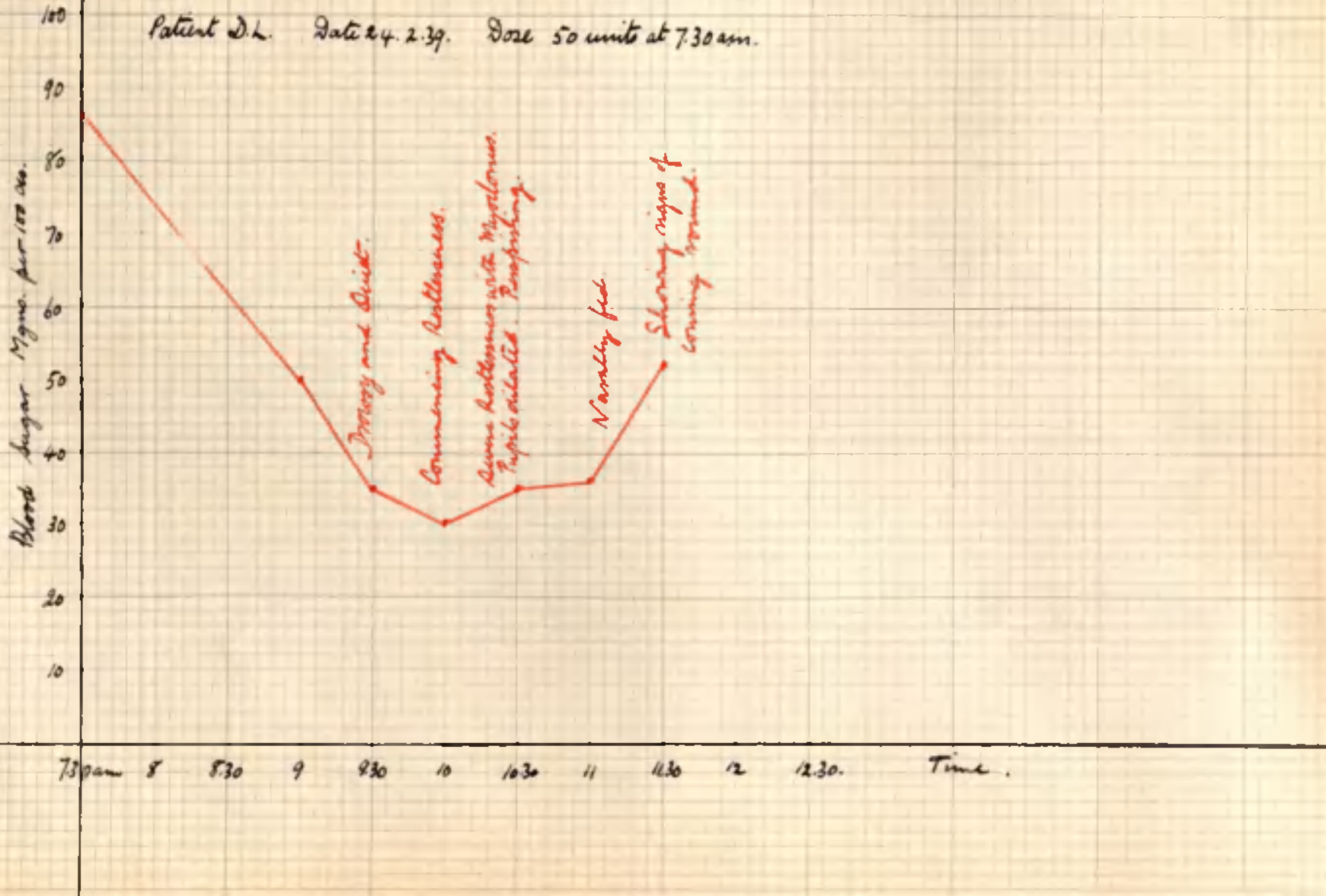
pressure/

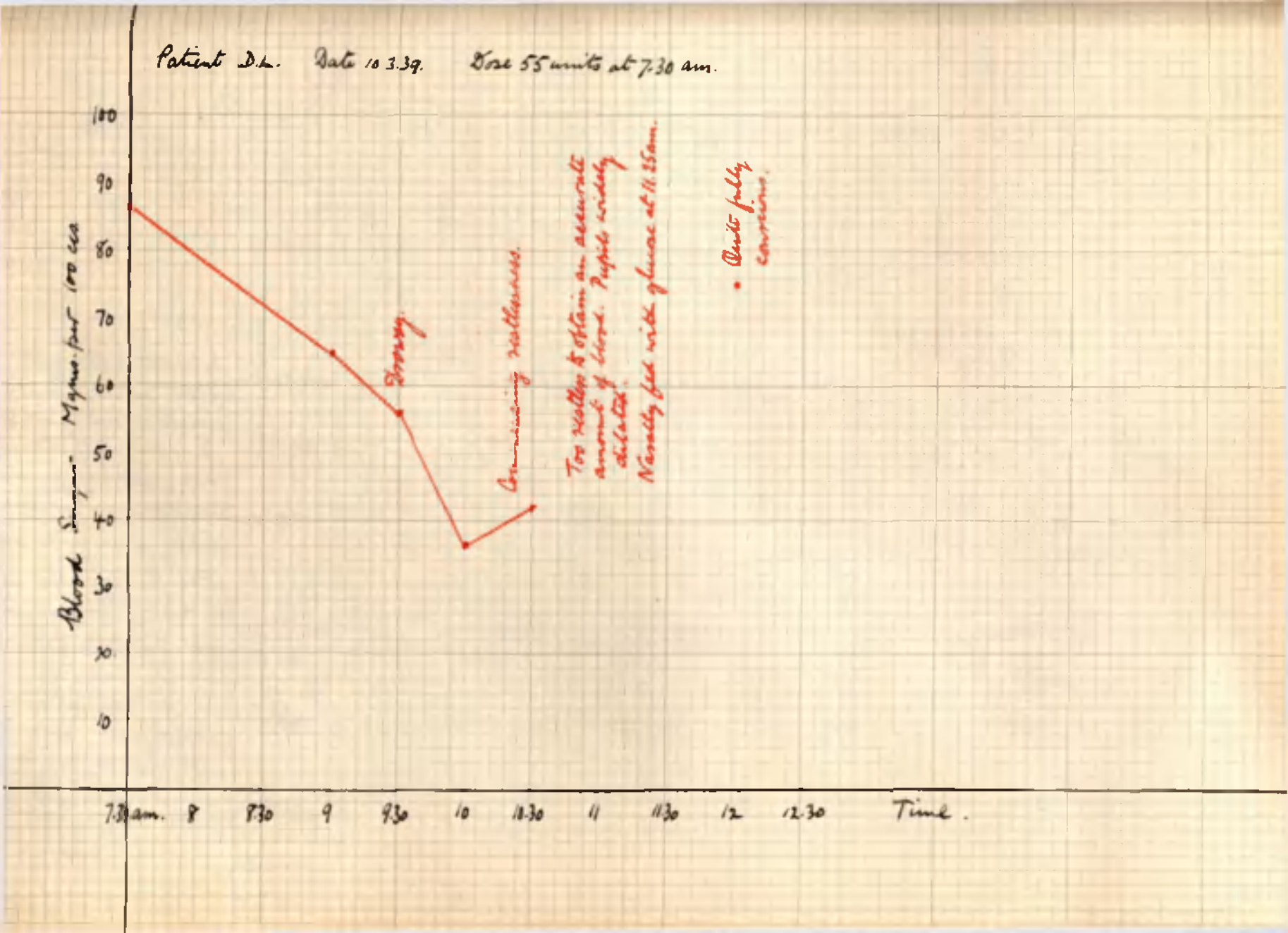
pressure are shown. The tendency appeared to be for both the systolic and diastolic pressures to rise during the restless myoclonic phase.

The weekly graph of the weight in this patient showed a definite upward curve.


Patient D.L. Date 3.1.39. Blood Sugar Tolerance Test.
160
150
140
130
120
110
100
90
80
70
60
50
Blood Sugar Mgms. per 100 cc.
Before Glucose
½
1
1½
2
2½
Hours.


Patient D.L. Date 7.2.39. Dose 45 units at 7.30 am.
Blood Sugar Mgms per 100 cc.
100
90
80
70
60
50
40
30
20
10
Quiet and Drowsy
Commencing Hallucinations with Mydriasis. Pupils dilated.
Restlessness continued.
Violently hot with glucose.
Quite conscious and able to converse.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time


Patient D.L. Date 24.2.39. Dose 50 units at 7.30 am.
Blood Sugar Mgms. per 100 cc.
100
90
80
70
60
50
40
30
20
10
Drowsy and Quiet.
Commencing Restlessness.
Severe Restlessness with Myoclonus. Typical diabetic Perspiring.
Markedly flat.
Showing signs of coming round.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30.
Time.


Patient D.L. Date 10 3.39. Dose 55 units at 7.30 am.
Blood Sugar - Mgms. per 100 cc
100
90
80
70
60
50
40
30
20
10
Drowsy.
Complaining restlessness.
Too restless to obtain an accurate amount of blood. Pupils widely dilated.
Visually fled with glucose at 11.25 am.
Quite fully conscious.
7.30 am.
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.

CHART

DISEASE

Name D. L.

Age

Diet

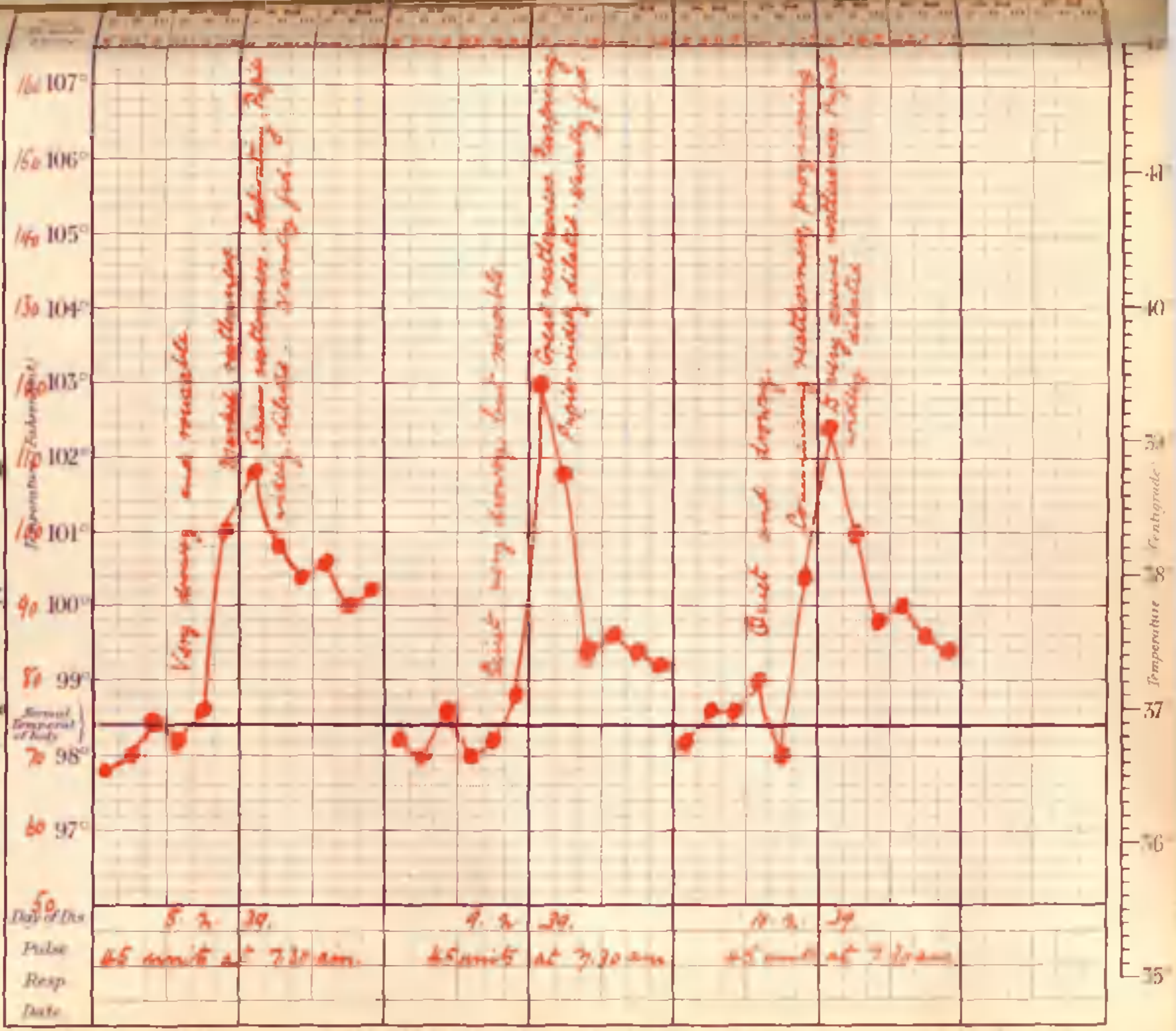
Case Book No.

Notes of Case

Three pulse records of the same patient. At 10 to 10.30 a.m. each morning, this ~~morning~~ patient became violently restless. She perspired and salivated. Pupils were widely dilated. She never went into a true deep coma but was unable to drink herself so had to be nasally fed. A marked tachycardia developed during the excited phase.

Date of admission

Result



Entered at Stationers' Hall

4 HOUR CHART

DISEASE

Name D.L.

Age

Diet

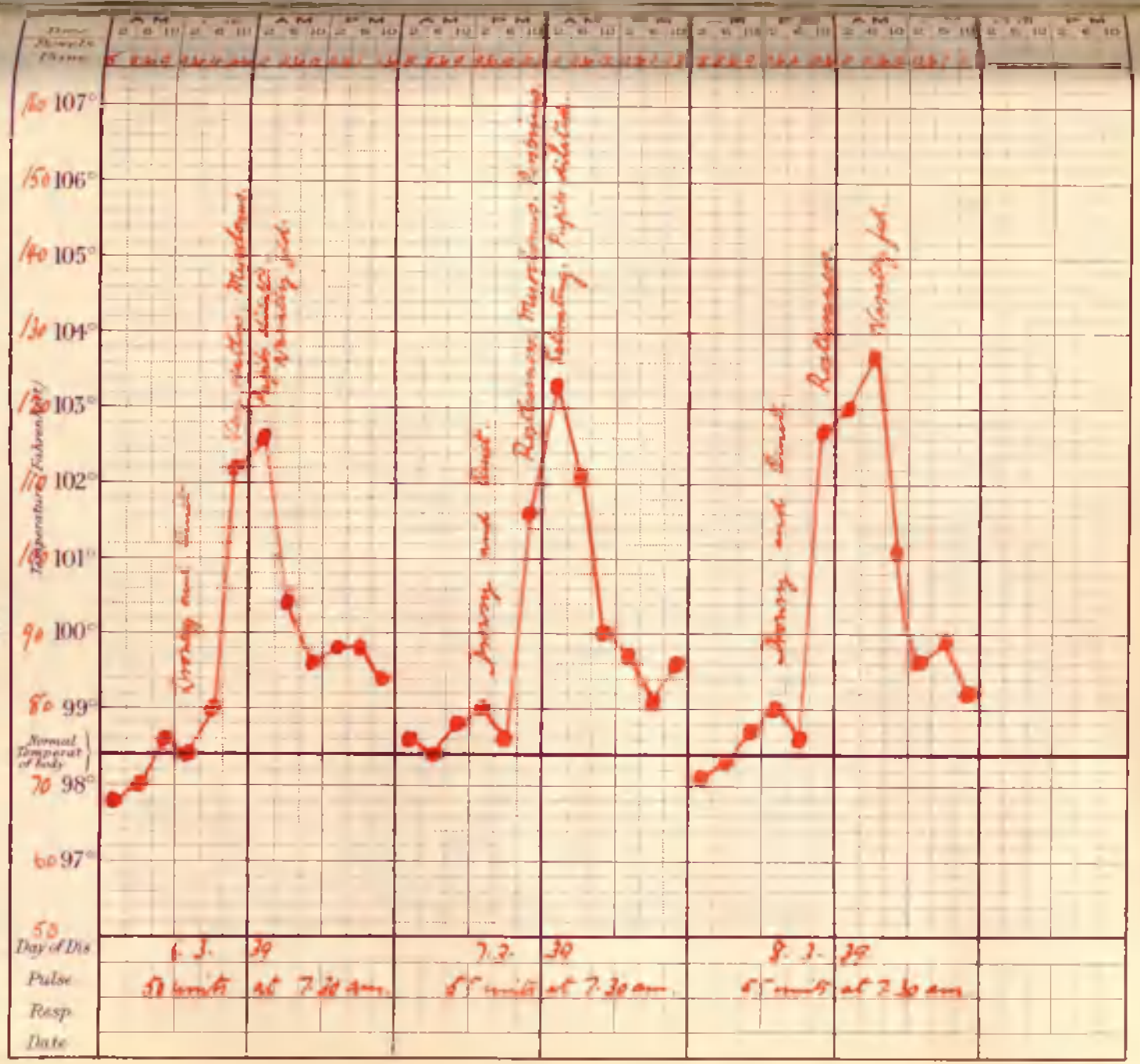
Case Book No.

Notes of Case

Three pulse records showing the tachycardia occurring during a very restless period and which occured everyday in this patient.

Date of admission

Result



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Goulds Clinical Chart

4 HOUR CHART

DISEASE

Name D.L.

Age

Diet

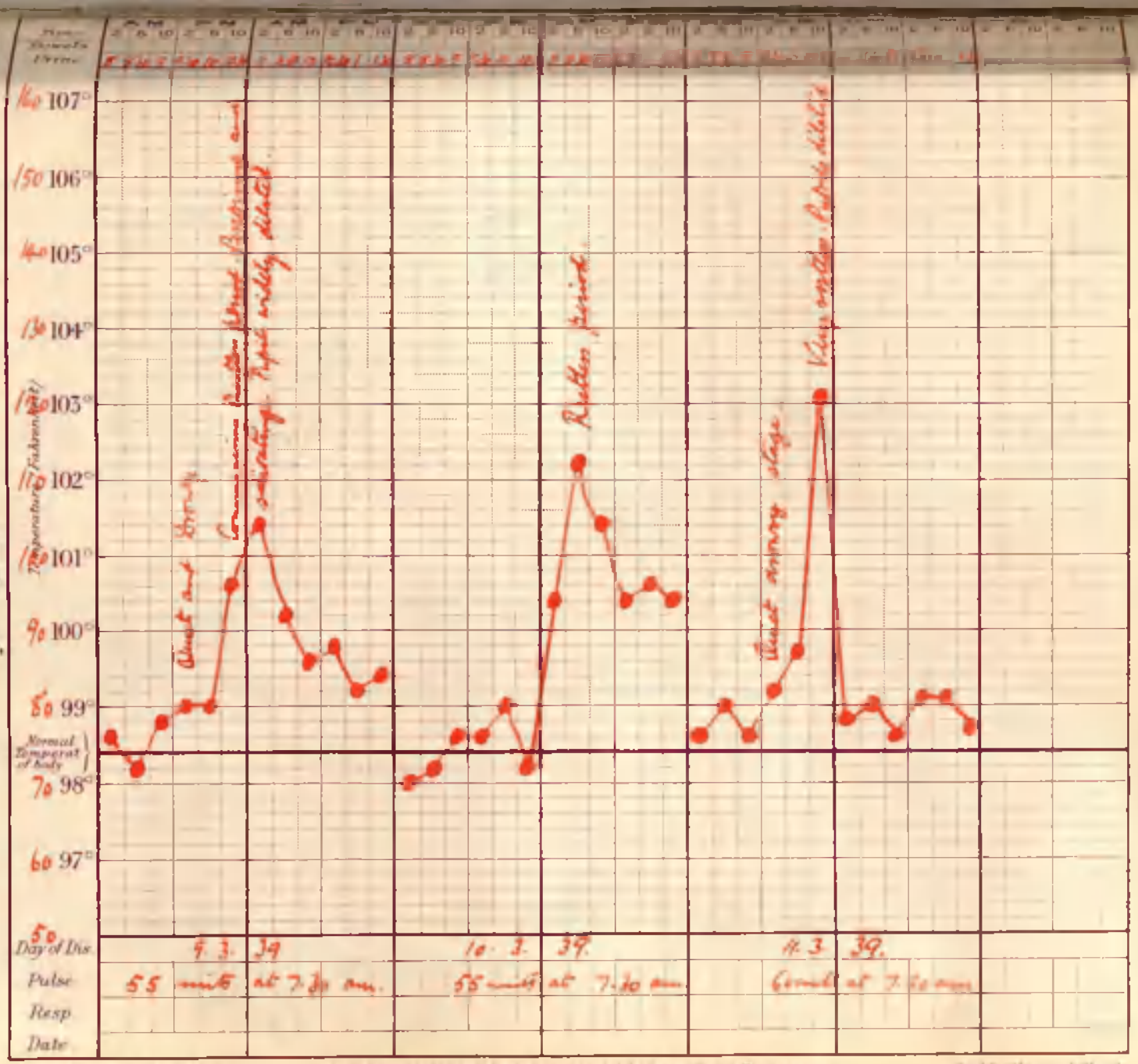
Case Book No.

Notes of Case

Three further pulse records showing the marked tachycardia taking place during a very restless phase, which occurred regularly every morning in this patient.

Date of admission

Result



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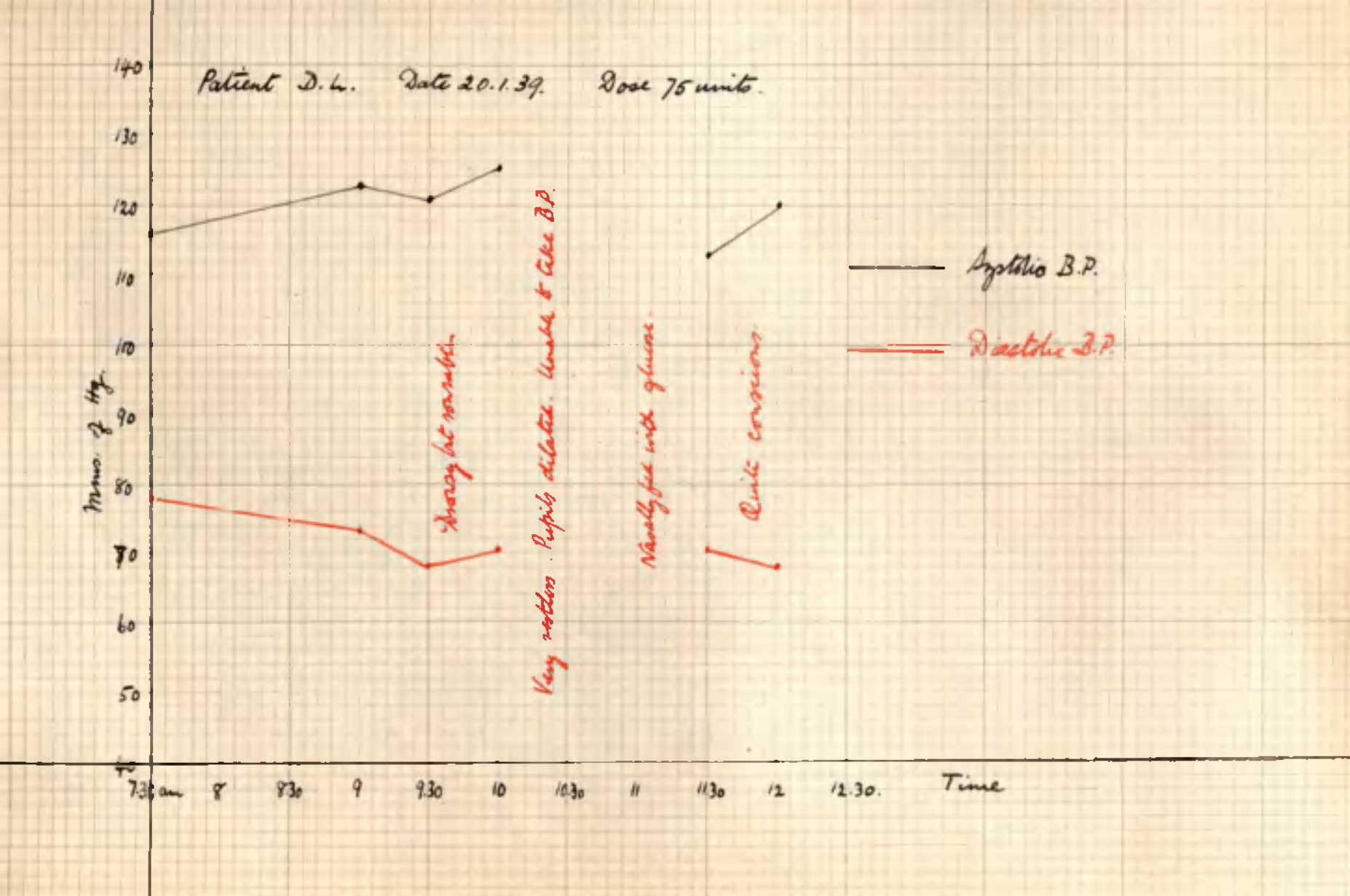
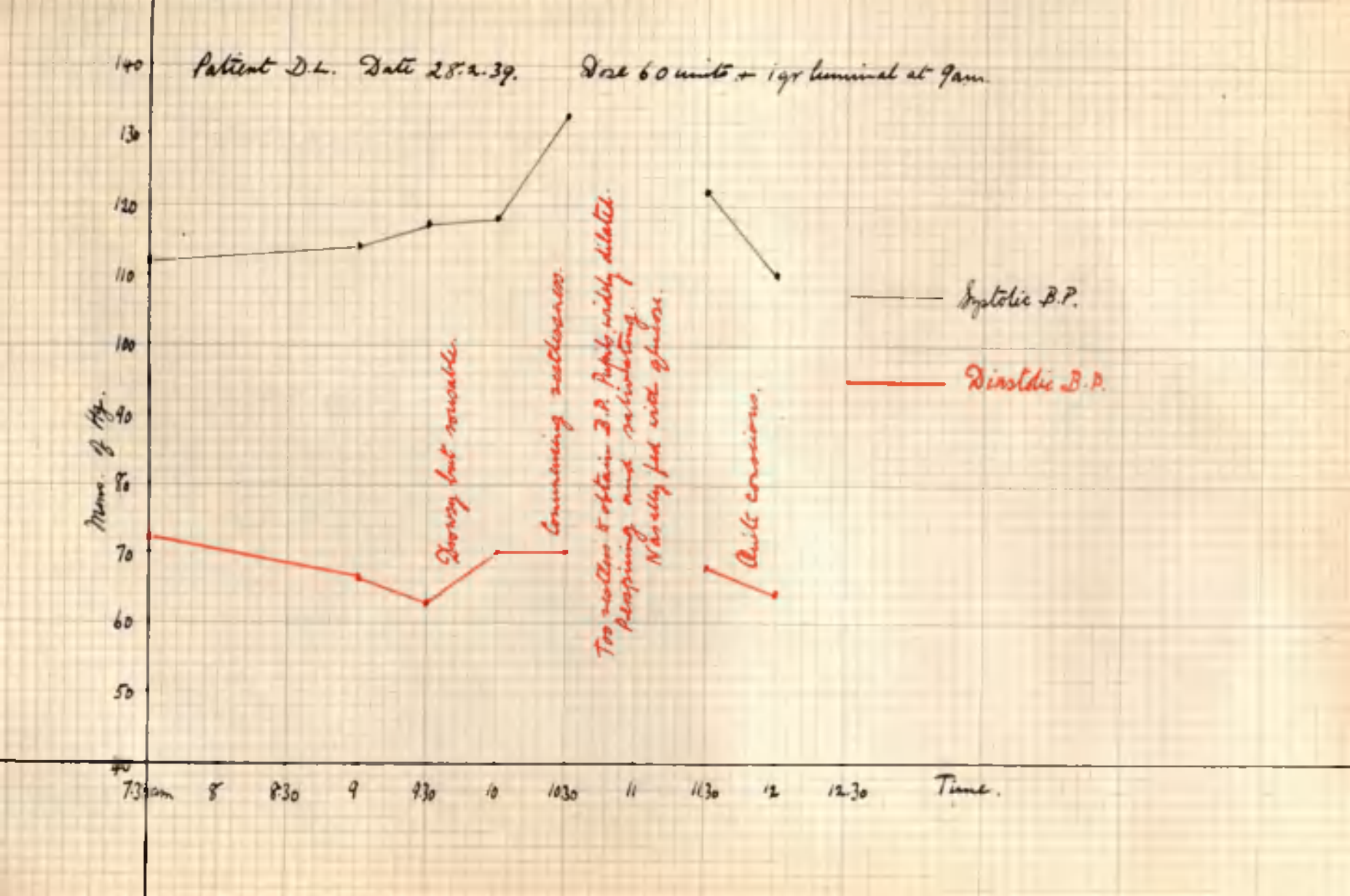
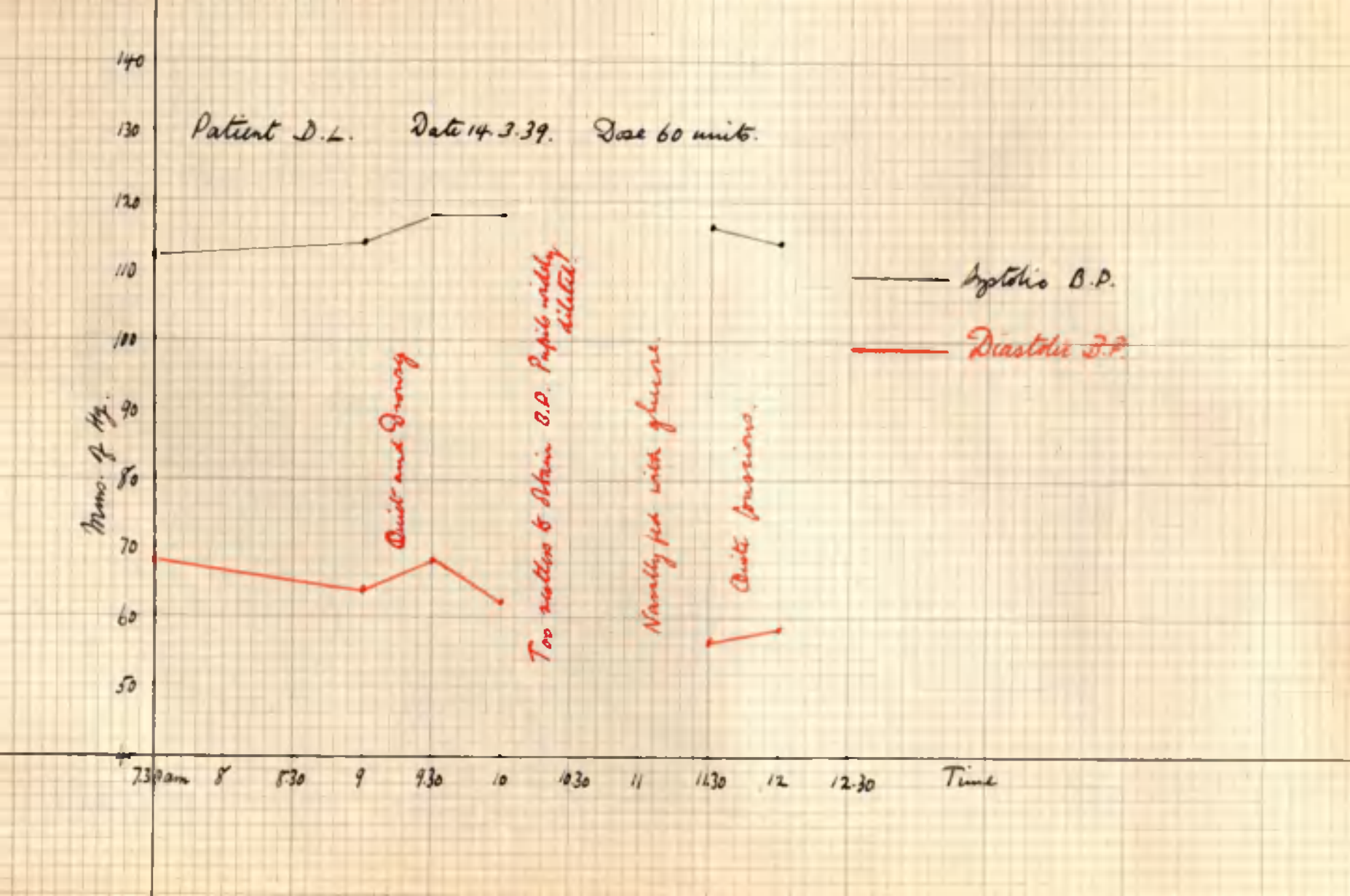
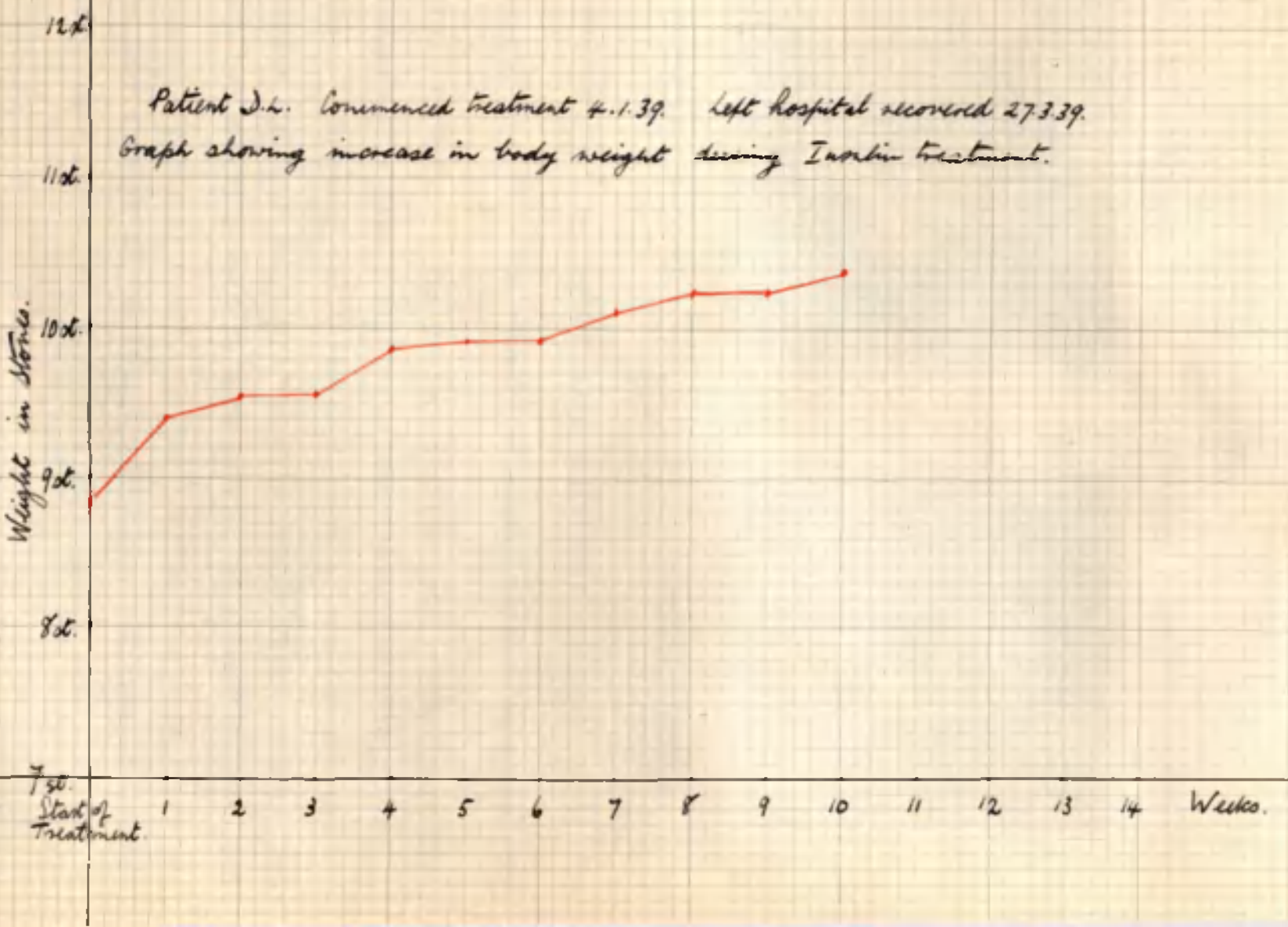
Gould's Clinical Chart


Patient D. L. Date 20.1.39. Dose 75 units.
mms. of Hg.
140
130
120
110
100
90
80
70
60
50
40
Systolic B.P.
Diastolic B.P.
Heavy but regular.
Very restless. Pupils dilated. Hands & face B.P.
Hardly fed with glucose.
Quite conscious.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30.
Time


Patient D.L. Date 28.2.39. Dose 60 units + 1gr luminal at 9am.
140
130
120
110
100
90
80
70
60
50
40
Mms. of Hg.
7.30am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.
Systolic B.P.
Diastolic B.P.
Drowsy but rousable.
Consciousness restored.
Too restless & obtain B.P. Pupils widely dilated. Perspiring and twitching. Normally but with glucose.
Quite conscious.


Patient D.L. Date 14.3.39. Dose 60 units.
140
130
120
110
100
90
80
70
60
50
mms. of Hg.
Systolic B.P.
Diastolic B.P.
Quite and Drowsy
Too restless & Active B.P. Pupils widely dilated
Normality but with glucose.
Quite Comatose.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time

Patient D.L. Commenced treatment 4.1.39. Left hospital recovered 27.3.39.
Graph showing increase in body weight during Insulin treatment.



C A S E 4.

M.J. Aged 19 years. Admitted July 12th., 1938.

Before treatment.

After treatment.

OCCUPATION. Cotton mill operative.

HEREDITY. No history of mental illness in ascendants.

PERSONAL HISTORY. The patient and her twin brother were the youngest of a family of five. Both mother and father were alive. In early childhood at 8 years of age the patient had measles and this was complicated by double Otitis media. This left her slightly deaf in both ears. At school she did well, reached the top standard. After leaving school at 14 years, she went to work in the cotton mill, kept the same job until her illness commenced, earning a wage of 20/- per week.

PRE-PSYCHOTIC PERSONALITY. Her mother described her as a cheerful girl who always had plenty of friends both at school and at work. She was very fond of her twin brother and preferred him to any of the other children. She was stubborn over trifles.

HISTORY of PRESENT ILLNESS. The onset was acute. She went to work on July 6th, 1938 but on July 7th she complained of headache and did not go to work. During the night of July 9th she got out of bed and tried to get out of the house in her night attire; on being restrained she became violent and started to scream as loud as she could. The next day she was removed to the Municipal hospital and was transferred to Whittingham on July 12th.

On admission her temperature was 99.8°F. and pulse 104. Her tongue was furred. Her left ear was discharging freely of thick pus, the ear drum was perforated; her right ear drum was also perforated. There was no swelling, redness or tenderness over either mastoid. Her throat was red and inflamed. The W.R. was negative and the C.S.F. report was negative. Mentally she was restless and resistive to all attention, she was unwilling to converse, she refused her food, appeared to be hallucinated and her habits were faulty.

She was given prontosil and her ear was irrigated

frequently/

frequently with hydrogen peroxide and in a short time her ear condition began to clear up.

The following notes indicated her progress in hospital.

AUGUST 22nd, 1938. "She is still unsettled, very restless and noisy, her habits are filthy, she is very troublesome with her food."

OCTOBER 10th, 1938. "There is no improvement in this patient, she is restless and excited, she destroys her bedlinen, she does not answer when spoken to. Her habits remain faulty and it is only with difficulty that she can be fed.

DECEMBER 21st, 1938. "Her bodily health is poor, she has become very emaciated, she has many septic sores over her body. Her left ear has commenced to discharge again. Mentally she appears to be worse and is deteriorating rapidly, she has been in a side room for a long time, her habits are filthy, she is resistive to nursing attention, frequently strikes out at the staff. She mutters and cries to herself appearing to be hallucinated."

MARCH 13th, 1939. "Her left breast is the site of a large intra-mammary abscess, this has been incised and a tube drain inserted. Her bodily health is very poor. Her left ear is still discharging."

MARCH 14th, 1939. "Pus from breast revealed pure growth of staphyllococcus aureus."

MARCH 27th, 1939. "The breast condition is clearing up, but the patient's mental condition is no better at all."

Although her physical condition was poor, it was decided to give her a course of insulin and treatment was commenced on April 13th, 1939 with a dose of 15 units. This was increased by ten units per day and on April 21st she had her first coma after a dose of 80 units. This was a typical wet coma, the patient passed into coma very quietly, there was no restless stage. Increased perspiration and profuse salivation were very marked.

The most noticeable change in this patient during the first fortnight of treatment was the change in her bodily appearance, she increased her weight from 6 st. 8 lbs. to 7 st. 3 lbs., her appetite improved and within three days of commencing treatment she was eating well. Prior to starting treatment her body was covered with septic sores and her left ear was discharging; in a fortnight most of the septic sores were healed and her ear had ceased to discharge. The only local treatment to her ear was a hydrogen peroxide irrigation and she had been having this same local treatment for many

weeks/

the last few weeks has been maintained both mentally and physically. The patient is well behaved, bright and cheerful. She is showing considerably more initiative and occupies herself usefully in the ward. She says that she realises she has been ill but is surprised that she has been here nearly a year as she does not remember coming here.

Treatment was eventually concluded on June 10th and the patient was discharged on June 27th. In all she had thirty eight comas.

This patient soon realised that the treatment was helping her and her only complaint was that when she woke following treatment she felt very uncomfortable owing to the bed being wet through from her perspiration.

PUPIL OBSERVATIONS.

(1) 28.4.39.	TIME.	SIZE.	OBSERVATIONS.
	7.30 a.m.	6 mms.	
	9.0 a.m.	6.5 mms.	
	9.30 a.m.	5 mms.	Drowsy.
	10.0 a.m.	4 mms.	Early coma, perspiring.
	11.0 a.m.	3 mms.	Deep coma, perspiring, salivating.
	11.50 a.m.	6.5 mms.	Awake after nasal feed.

(2) 29.4.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	6.5 mms.	
9.10 a.m.	6 mms.	
9.50 a.m.	6 mms.	Drowsy.
10.30 a.m.	4 mms.	Early coma, perspiring.
10.55 a.m.	3 mms.	Deep coma, perspiring, salivating. Slow pulse 62. When patient was stimulated, after a latent period of 1-2 secs. the pupils dilated up to 7.5 mms., remained so for 20 secs. and then contracted again. At the same time, the pulse rate increased and then slowed down again.
11.15 a.m.	3 mms.	
12 noon	7 mms.	Awake after nasal feed.

(3) 1.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	6.5 mms.	
9.0 a.m.	5.0 mms.	Drowsy and quiet.
10.0 a.m.	4.0 mms.	Early coma, perspiring.
10.25 a.m.	3.0 mms.	Deep coma, perspiring, salivating.
11.10 a.m.	3.0 mms.	Slow pulse 62.
11.40 a.m.	7.0 mms.	Awake after nasal feed.

(4) 2.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	5.5 mms.	Drowsy and quiet.
10.15 a.m.	4.5 mms.	Early coma, perspiring.
11.0 a.m.	3 mms.	Deep coma. Slow pulse 66. Stimulation of patient produced a dilatation of the pupils after a latent period of 1-2 secs., after 15-20 secs. the pupils contracted again.
11.43 a.m.	6 mms.	Awake after nasal feeding.

(5) 3.5.39.

TIME.	SIZE.	OBSERVATIONS.
9.0 a.m.	5.5 mms.	
9.30 a.m.	5 mms.	Drowsy and quiet.
10.0 a.m.	5 mms.	Very drowsy. Some perspiration.
10.20 a.m.	3.5 mms.	Early coma, perspiring freely.
10.50 a.m.	3 mms.	Deep coma. Perspiring, salivating.
11.15 a.m.	3 mms.	Slow pulse 60. Pupils dilated on stimulation and pulse rate increased.
11.50 a.m.	7 mms.	Awake after nasal feeding.

(6) 5.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	6 mms.	
9.0 a.m.	6 mms.	
9.40 a.m.	5.5 mms.	Drowsy.
10.15 a.m.	4 mms.	Early coma. Perspiring.
10.55 a.m.	3 mms.	Deep coma, perspiring freely.
11.20 a.m.	3 mms.	Salivating. Slow pulse 62.
12 noon	6.5 mms.	Awake after nasal feeding.

(7) 12.5.39.

TIME.	SIZE.	OBSERVATIONS.
10.0 a.m.	5 mms.	Very drowsy and quiet.
10.30 a.m.	4 mms.	Coma.
11.0 a.m.	3 mms.	Deep coma. Slow pulse 64.
11.40 a.m.	6 mms.	Awake after nasal feed.

(8) 13.5.39.

TIME.	SIZE.	OBSERVATIONS.
9.0 a.m.	6 mms.	
10.0 a.m.	4 mms.	Very drowsy, perspiring.
10.20 a.m.	3 mms.	Coma.
10.40 a.m.	3 mms.	Deep coma, perspiring and salivating freely. Slow pulse 60. Pupils
11.15 a.m.	3 mms.	dilated up to 7.5 mms. after stimulation. After 20 secs. the pupils contracted again. At the same time the pulse rate quickened and then slowed.
11.50 a.m.	6.5 mms.	Awake after nasal feeding.

(9) 16.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	6.5 mms.	
9.0 a.m.	6 mms.	Drowsy.
10.10 a.m.	4.5 mms.	Early coma. Perspiring.
10.45 a.m.	3 mms.	Deep coma. Perspiring, salivating.
11.0 a.m.	3 mms.	Slow pulse 64.
11.45 a.m.	7 mms.	Awake after nasal feed.

(10) 17.5.39.

TIME.	SIZE.	OBSERVATIONS.
9.0 a.m.	6 mms.	
9.30 a.m.	5.5 mms.	Drowsy and quiet.
10.0 a.m.	4.5 mms.	Early coma.
11.0 a.m.	3 mms.	Deep coma. Slow pulse 62.
11.35 a.m.	6.5 mms.	Awake after nasal feed.

(11) 18.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	6 mms.	
9.25 a.m.	5 mms.	Drowsy and quiet. Some perspiration.
10.0 a.m.	4 mms.	Early coma, perspiring.
10.25 a.m.	3 mms.	Deep coma, perspiring and salivating freely.
11.0 a.m.	3 mms.	Pupils watched continuously for the next 10 mins., remained small all the time.
11.50 a.m.	7 mms.	Awake after nasal feed.

(12) 19.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	6.5 mms.	
9.0 a.m.	6 mms.	
10.0 a.m.	4 mms.	Early coma, perspiring.
10.15 a.m.	3.5 mms.	Perspiring and salivating.
10.40 a.m.	3 mms.	Deep coma. Slow pulse 60. Following stimulation and after a latent period of 1-2 secs. the pupils dilated up to 7 mms., after 15 secs. they contracted again.
11.45 a.m.	7 mms.	Awake after nasal feed.

After the morning injection there was a gradual contraction of the pupils until during deep coma the pupils were very small; however if at this stage the patient was disturbed the pupils dilated after a latent period of 1-2 secs., this dilatation lasted from fifteen to twenty seconds and was then replaced by the contracted stage. Accompanying this dilatation there was a temporary speeding up of the pulse.

BLOOD SUGAR OBSERVATIONS.

A blood sugar tolerance test and four graphs of the blood sugar following insulin are shown. Interesting points were :

(1) In the blood sugar tolerance test, the blood sugar values at 1 hour and 1½ hours after drinking the glucose were higher than what is regarded as normal. There was, however, a return to normal values in the normal time.

(2) As usual following the injection of insulin, the greatest fall in the blood sugar took place in the first one and a half to two hours, when apart from drowsiness and occasionally some perspiration there were no symptoms.

(3) The commonest level for coma appeared to lie between 20 and 35 mgms. per 100 ccs.

(4) In two out of the four graphs, the blood sugar level during deep coma was slightly higher than it was during early coma.

(5) As usual the patient was fully conscious after nasal feeding and yet her blood sugar level was not so high as it was when the morning's treatment was started.

PULSE RATE OBSERVATIONS.

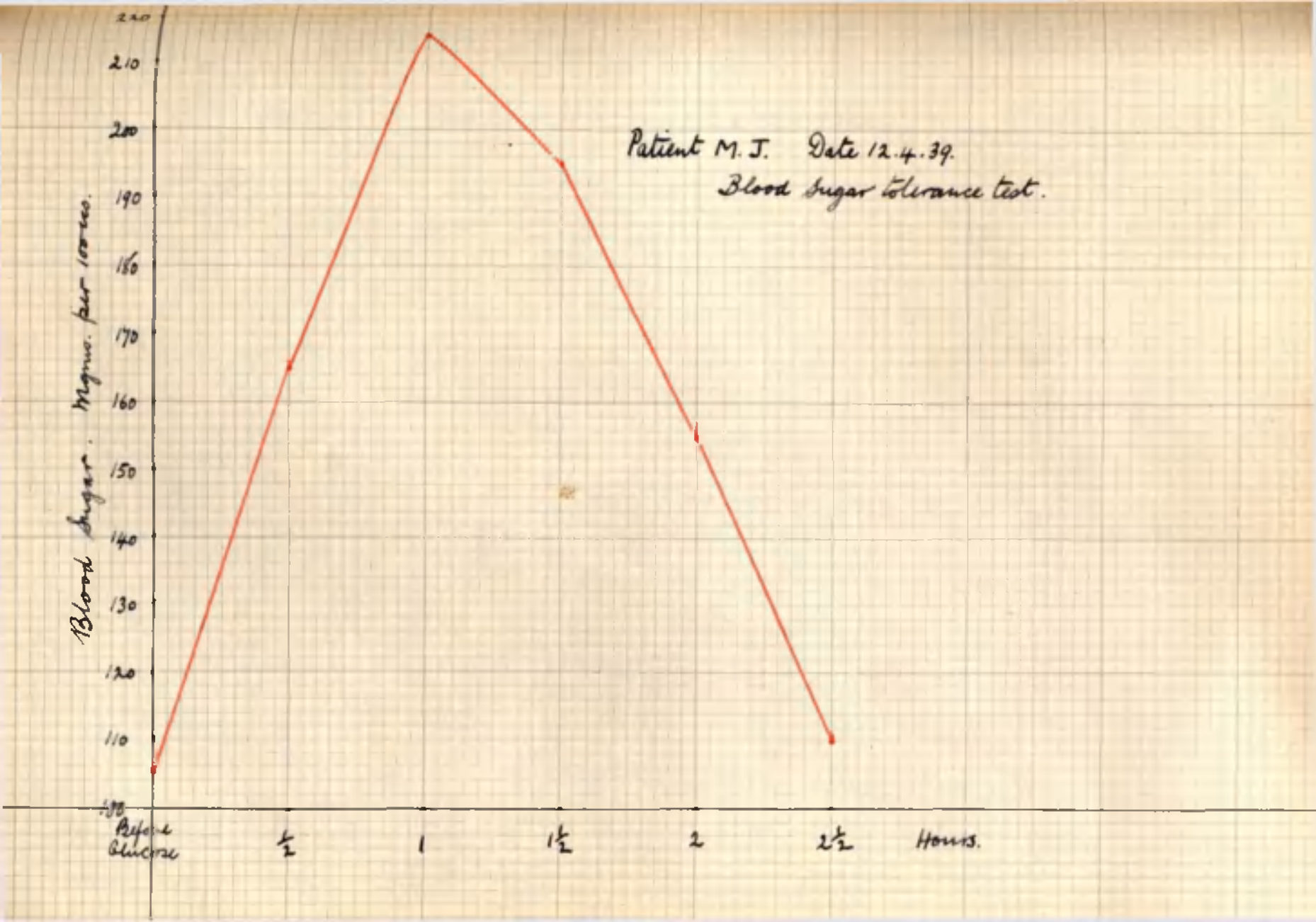
Nine of the daily charts are shown. In all an initial tachycardia was noticed and this developed although the/

the patient was lying drowsy and quiet. Following the onset of coma, the pulse rate slowed and became very slow at the time of deep coma. Following the nasal feed and as the patient came round there was a speeding up of the pulse again.

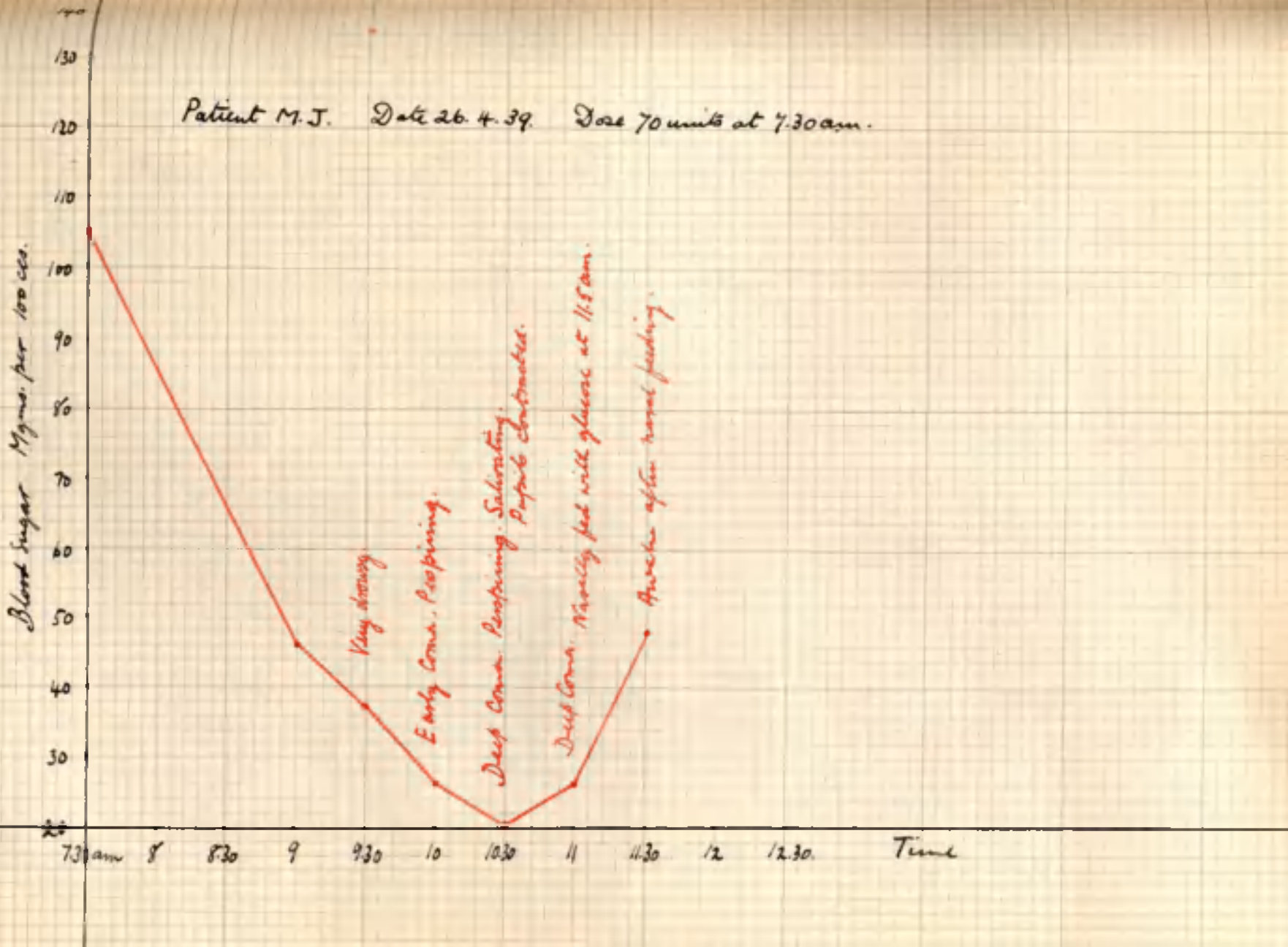
BLOOD PRESSURE OBSERVATIONS.

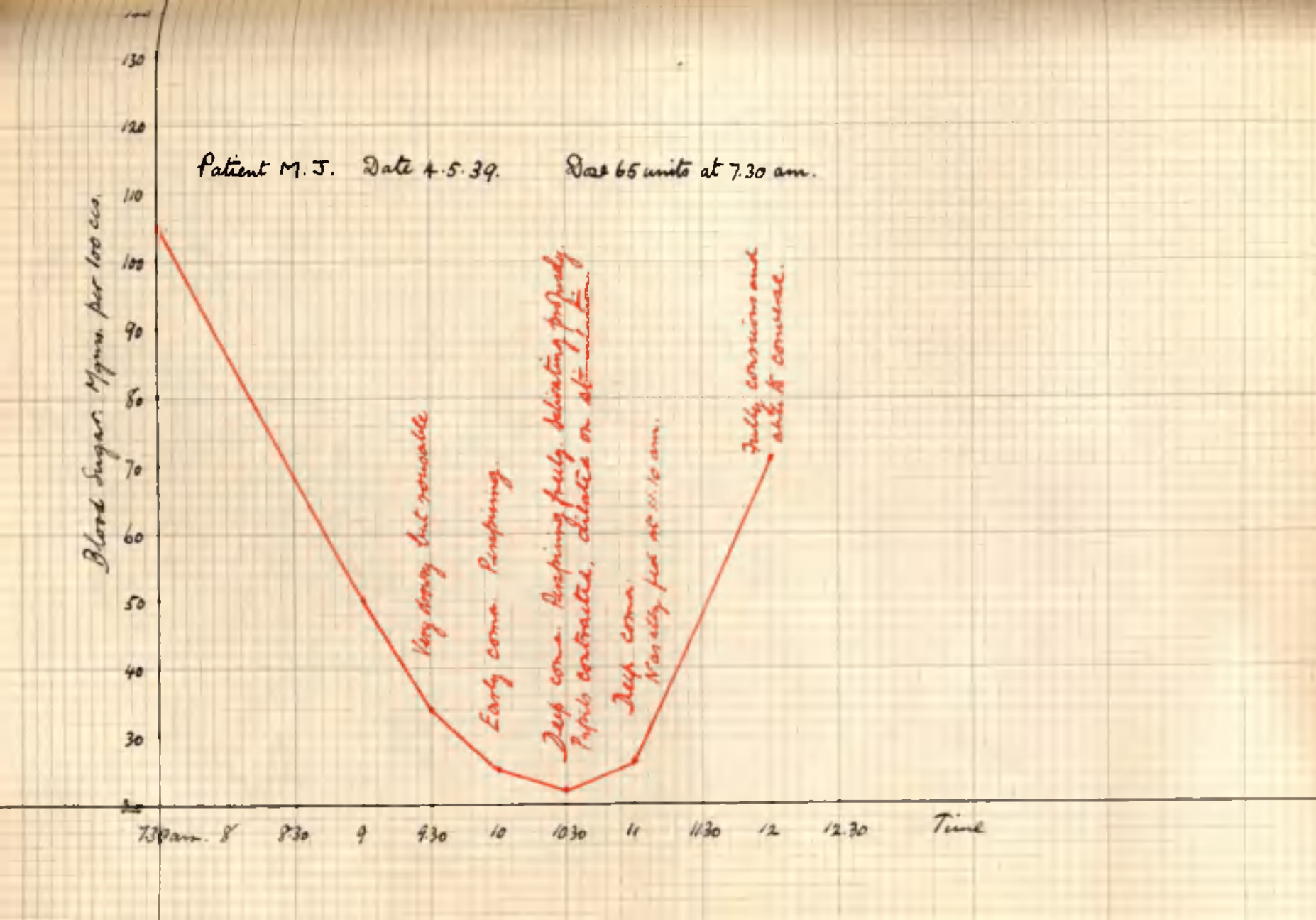
Six graphs of the systolic and diastolic pressures are shown following the injection of insulin. In this patient who passed into coma very quietly, there was at first a rise in both systolic and diastolic pressures, the rise in the systolic pressure was greater than in the diastolic; this rise was followed by a fall in both as a wet type of coma developed; the fall in the diastolic was greater than the fall in the systolic. The pulse pressure was increased. On two occasions the diastolic pressure fell to 0 and at this time, perspiration was very profuse. After nasal feeding with glucose, both systolic and diastolic pressure rose again to what appeared to be the normal figure for the patient lying in bed.

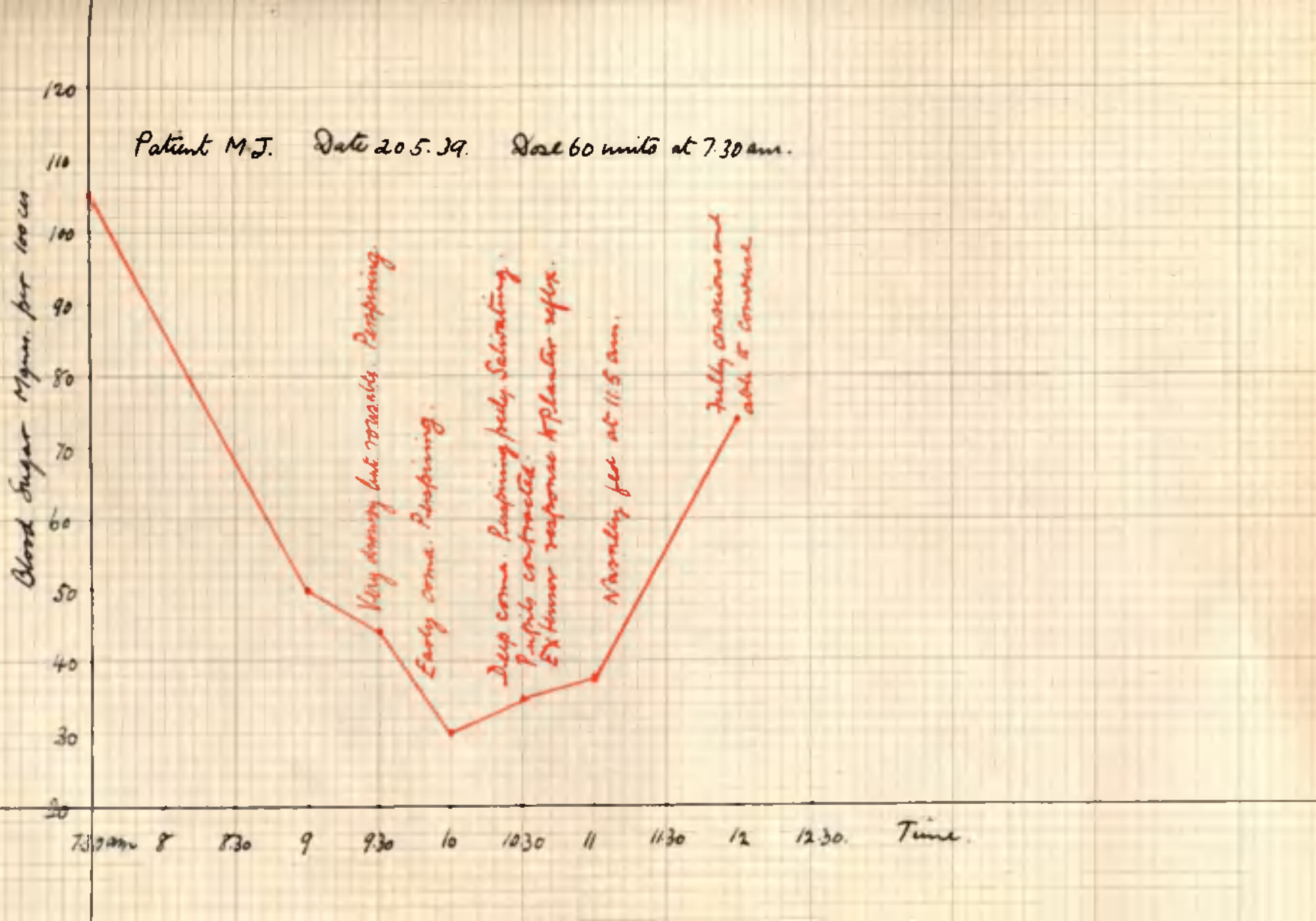
The weekly weight graph in this patient showed a definite upward curve.

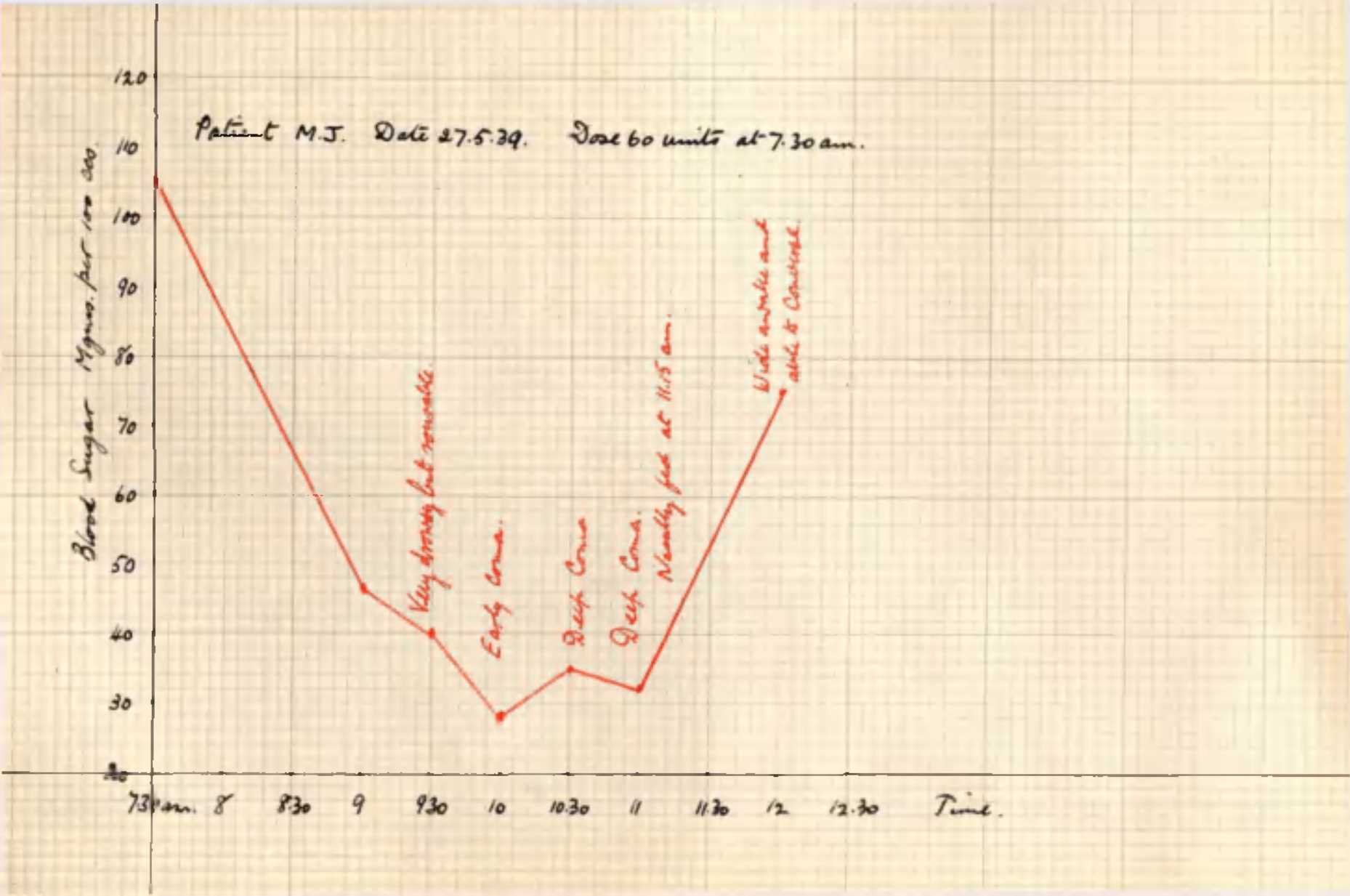

Patient M. J. Date 12.4.39.
Blood sugar tolerance test.
Blood sugar. Mgms. per 100 cc.
220
210
200
190
180
170
160
150
140
130
120
110
100
Before Glucose
½
1
1½
2
2½
Hours.

Patient M.J. Date 26.4.39. Dose 70 units at 7.30 am.




Patient M.J. Date 4.5.39. Dose 65 units at 7.30 am.
Blood Sugar Mgms. per 100 cc.
130
120
110
100
90
80
70
60
50
40
30
Very drowsy but rousable
Early coma. Perspiring.
Deep coma. Perspiring freely. Respirations deliberate, stertorous
Pupils contracted, dilated on stimulation
Deep coma.
Normality just reached at 10.45 am.
Fully conscious and able to converse.
7.30 am. 8 8.30 9 9.30 10 10.30 11 11.30 12 12.30 Time


Patient M.J. Date 20.5.39. Dose 60 units at 7.30 am.
Blood Sugar Mgms. per 100 cc
120
110
100
90
80
70
60
50
40
30
20
Very drowsy but rousable. Perspiring.
Early coma. Perspiring.
Deep coma. Perspiring/pulse. Salivating.
Pupils contracted.
Ex. Hour response to Plantar reflex.
Normality fee at 11.5 am.
Fully conscious and able to converse.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.


Patient M.J. Date 27.5.39. Dose 60 units at 7.30 am.
Blood Sugar Mgms. per 100 cc.
120
110
100
90
80
70
60
50
40
30
20
Very drowsy but rousable.
Early Coma.
Deep Coma
Deep Coma.
Normality fast at 11.15 am.
Under anaesthetic and about to Convulse.
7.30 am.
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.

4 HOUR CHART

DISEASE

Name M. J.

Age

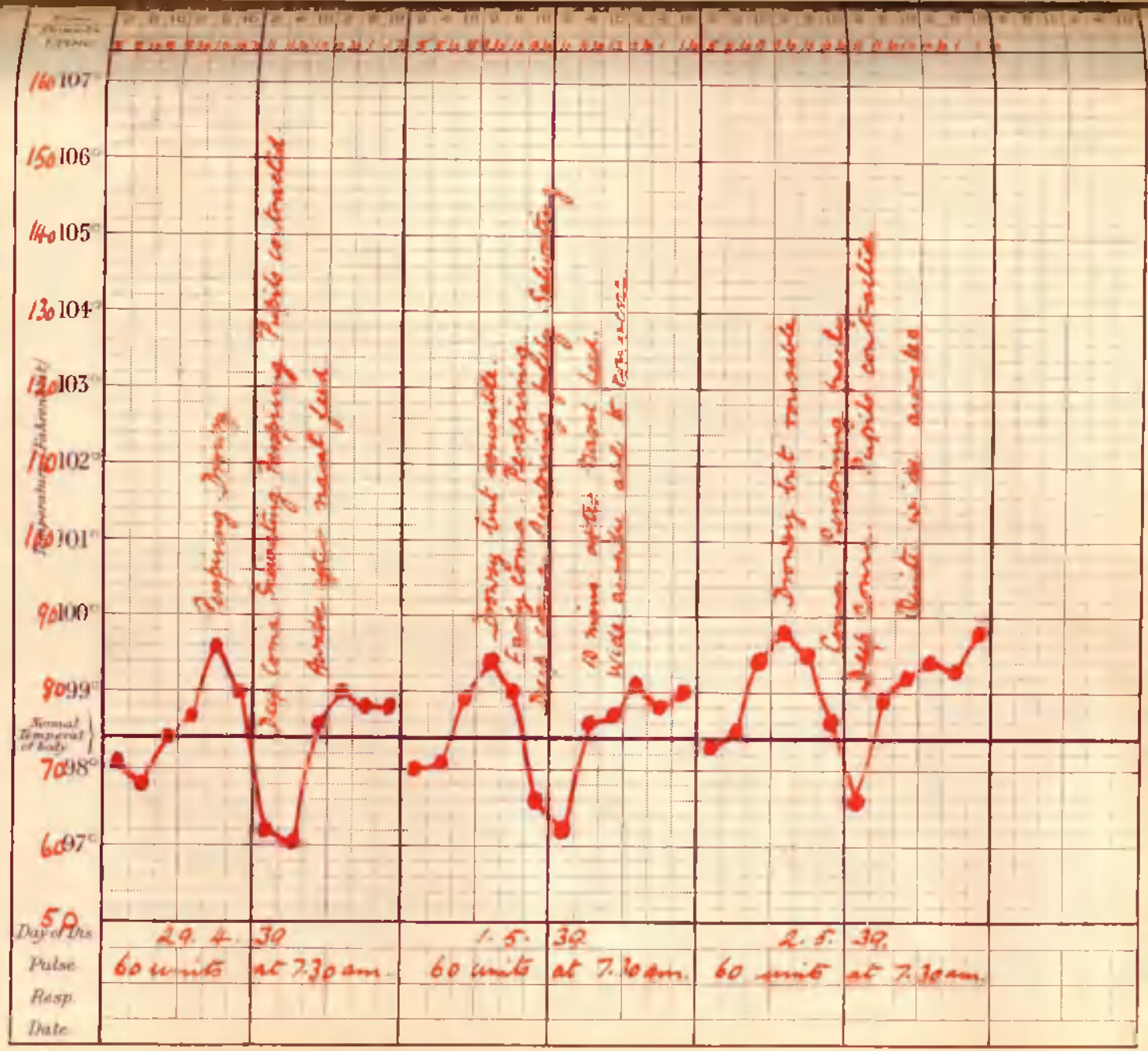
Diet

Case Book No.

Notes of Case

Date of admission

Result



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4 HOUR CHART

DISEASE

Name M. J.

Age

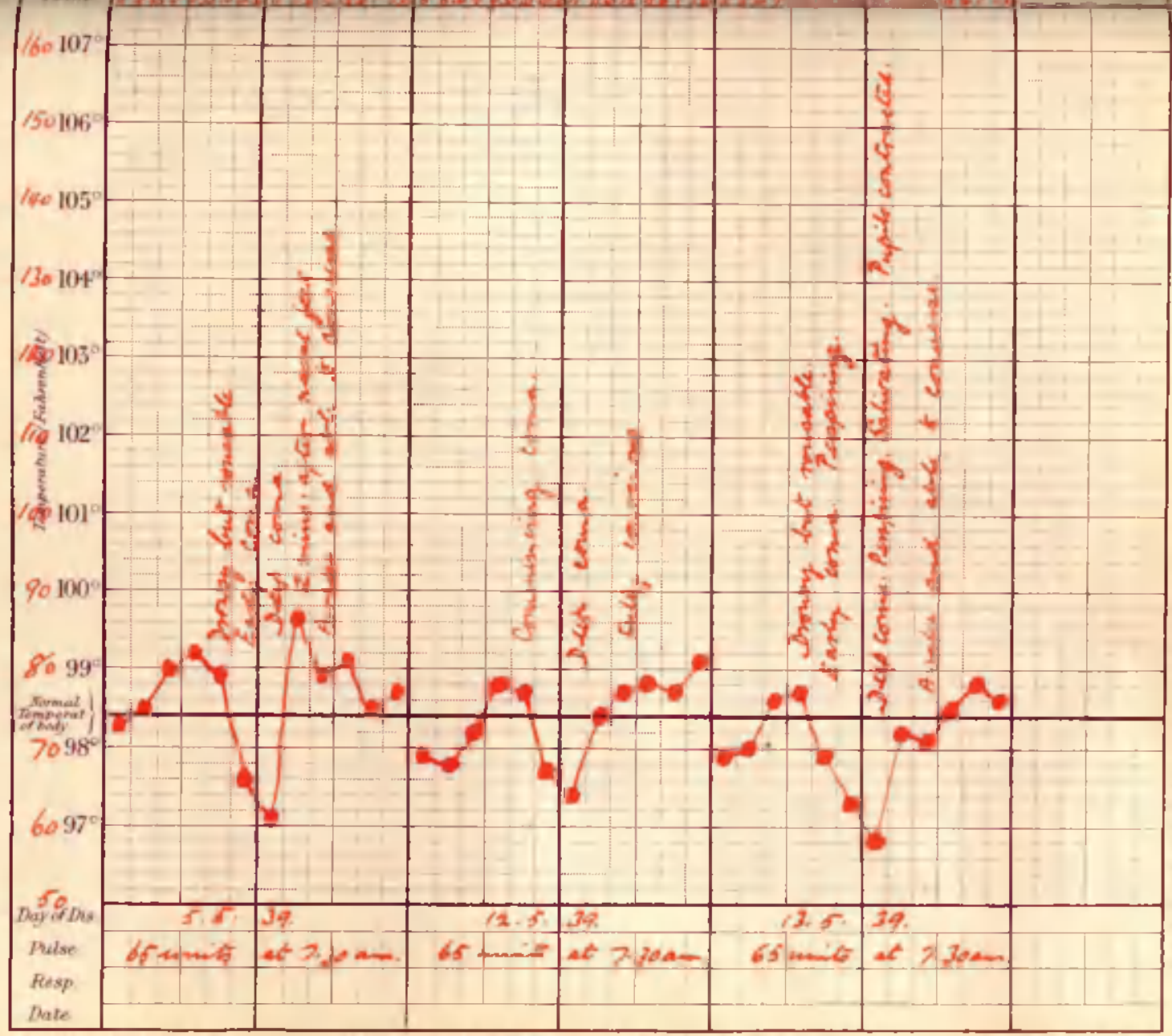
Diet

Case Book N°

Notes of Case

Date of admission

Result



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4 HOUR CHART

DISEASE

Name { M.J.

Age

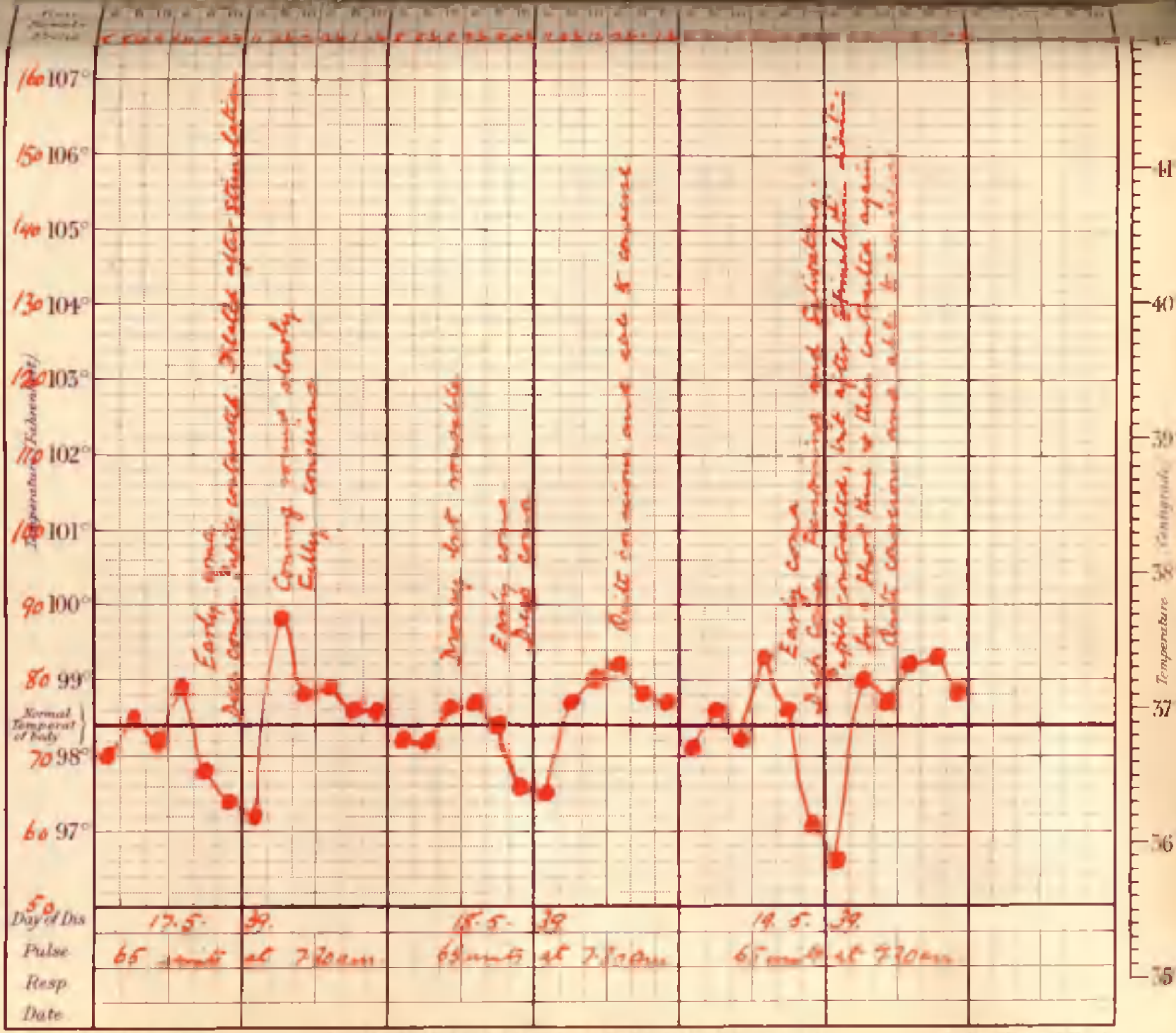
Diet

Case Book No

Notes of Case

Date of admission

Result



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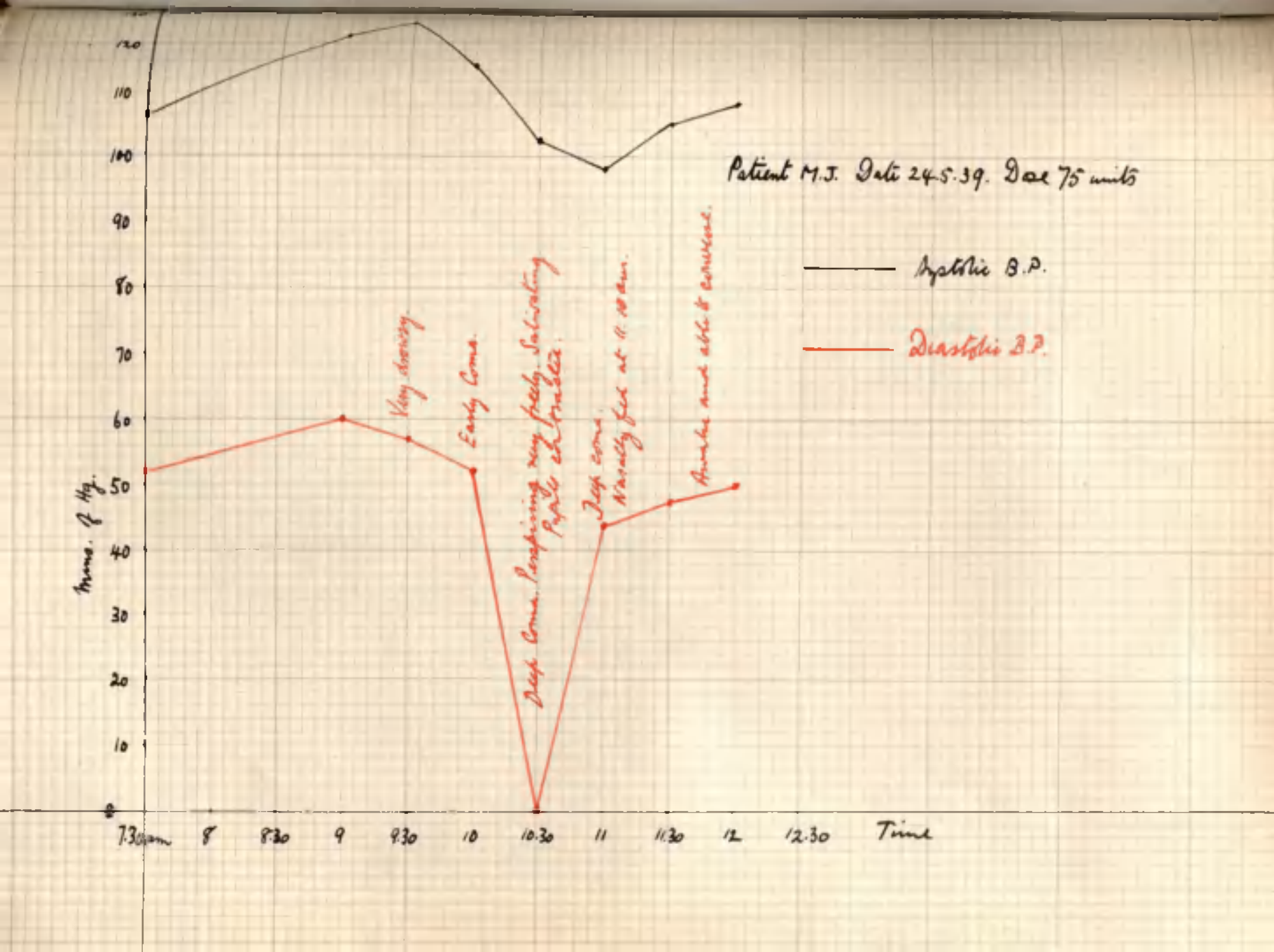
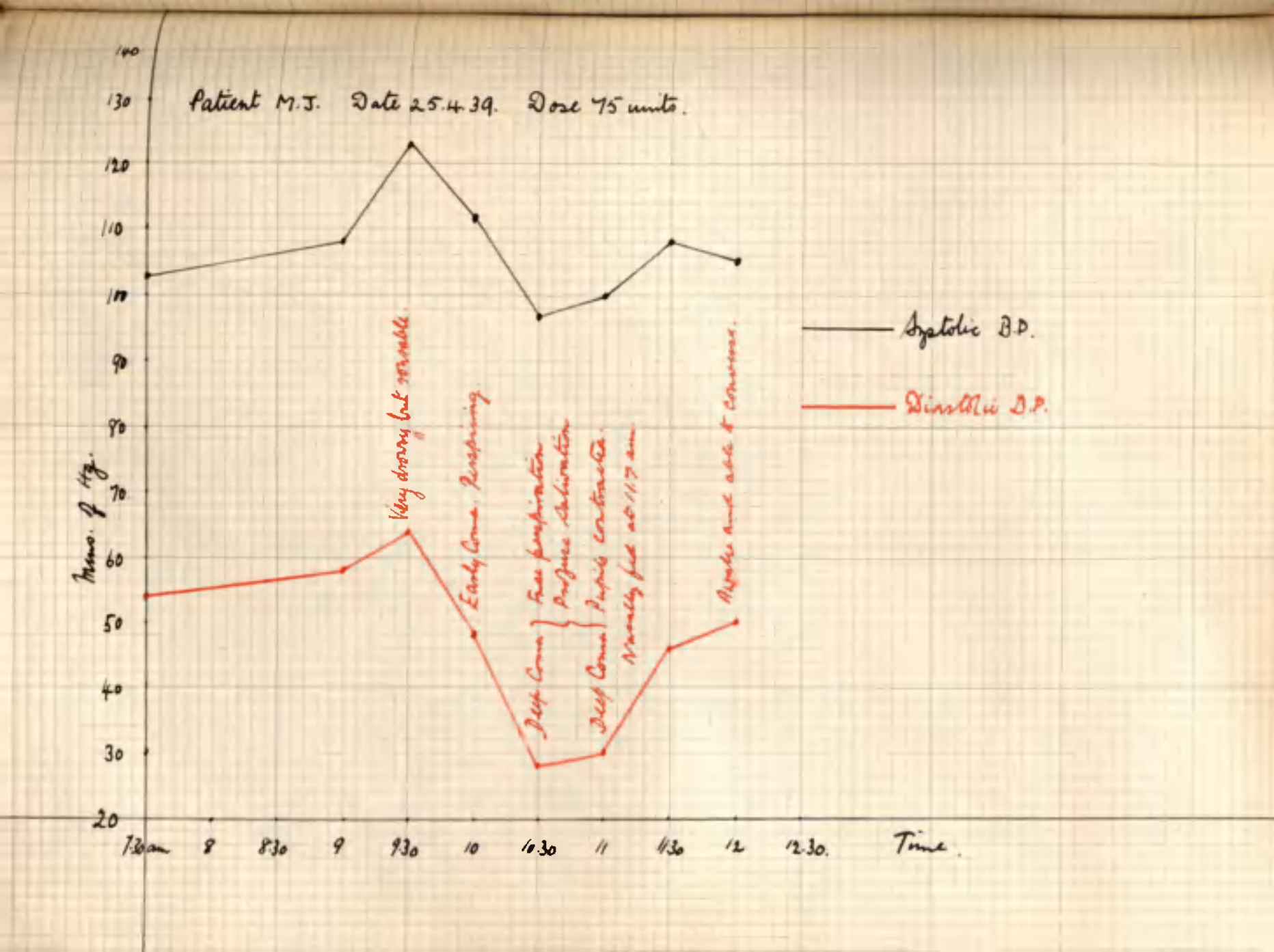
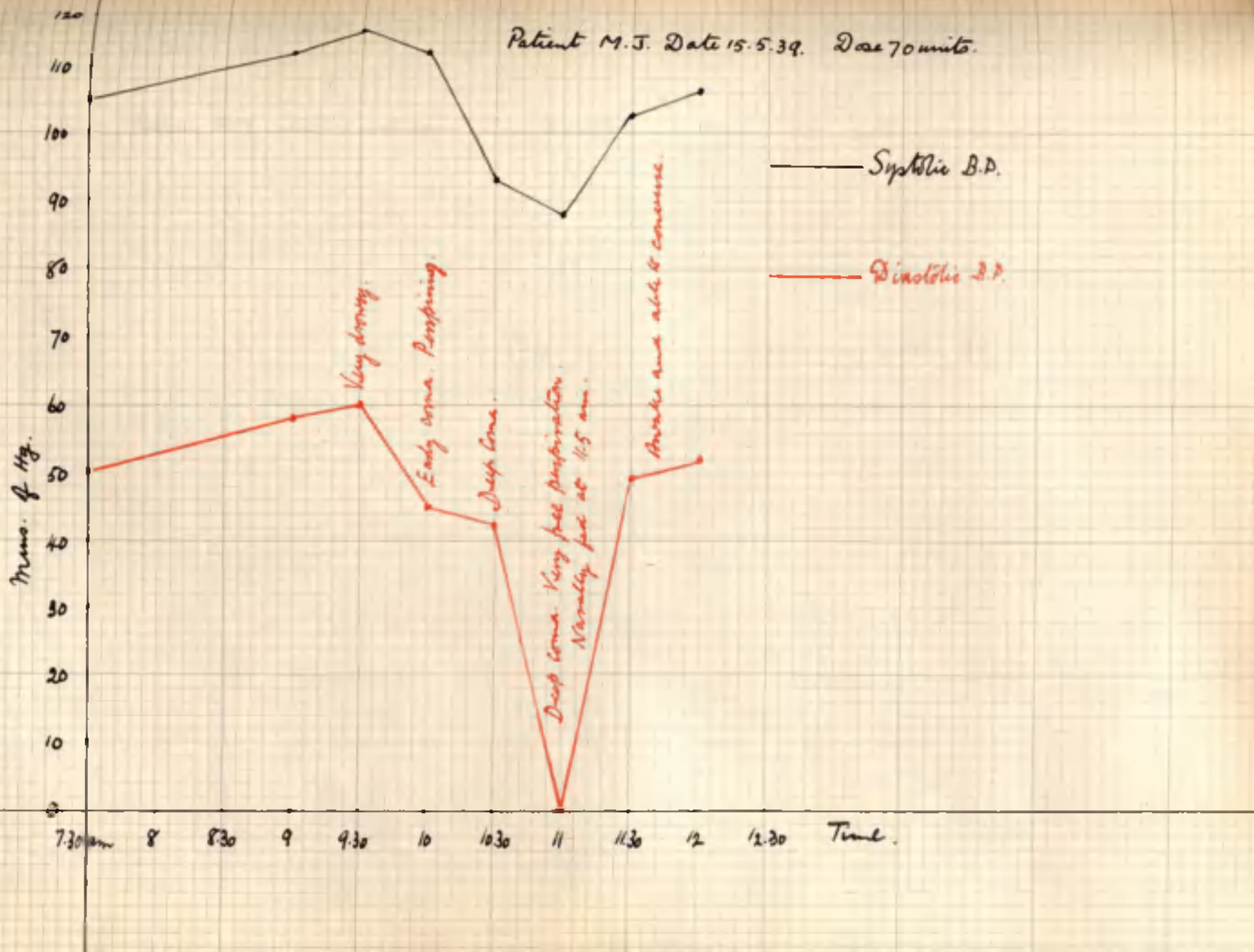
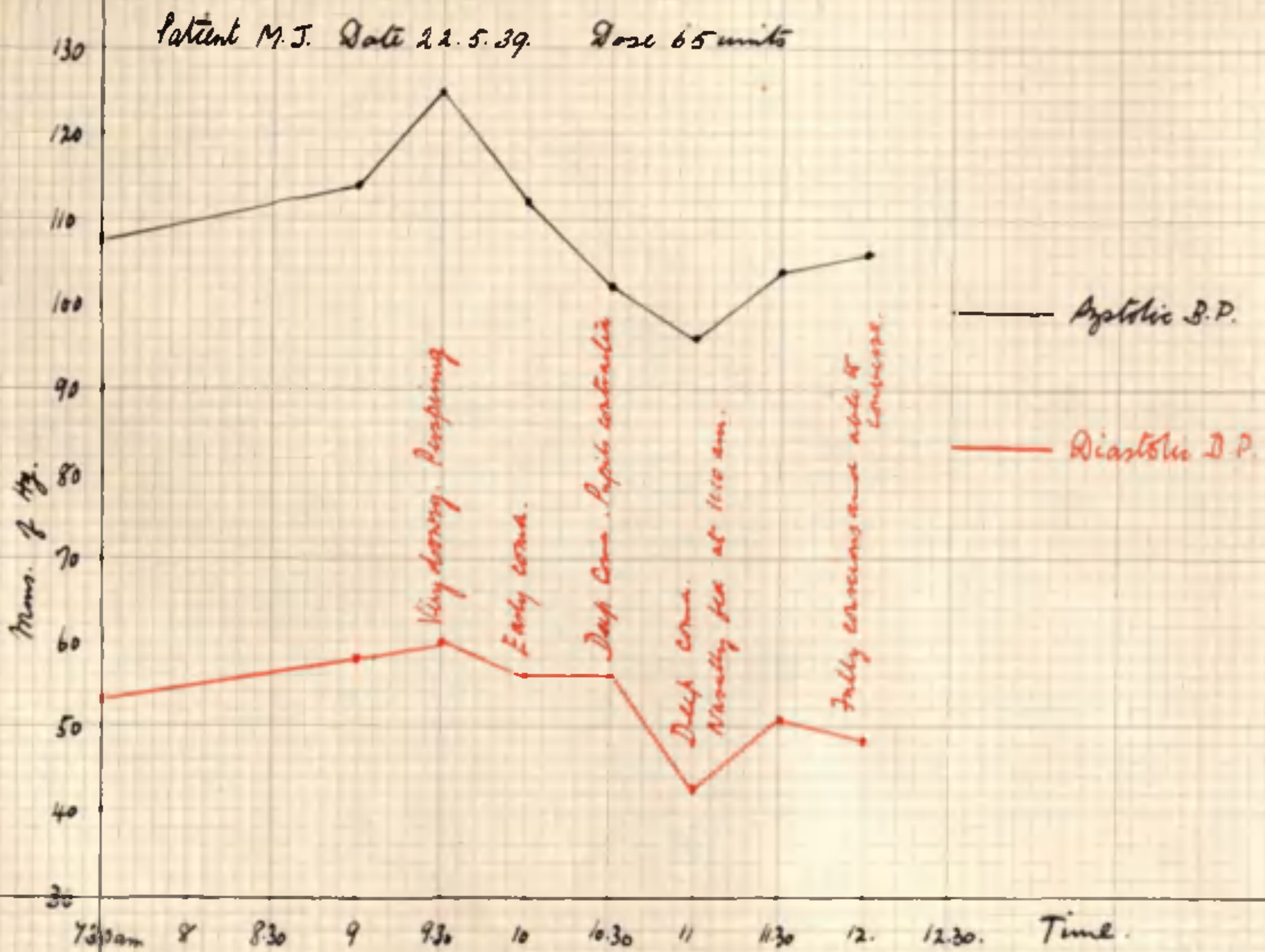
Gould's Clinical Chart

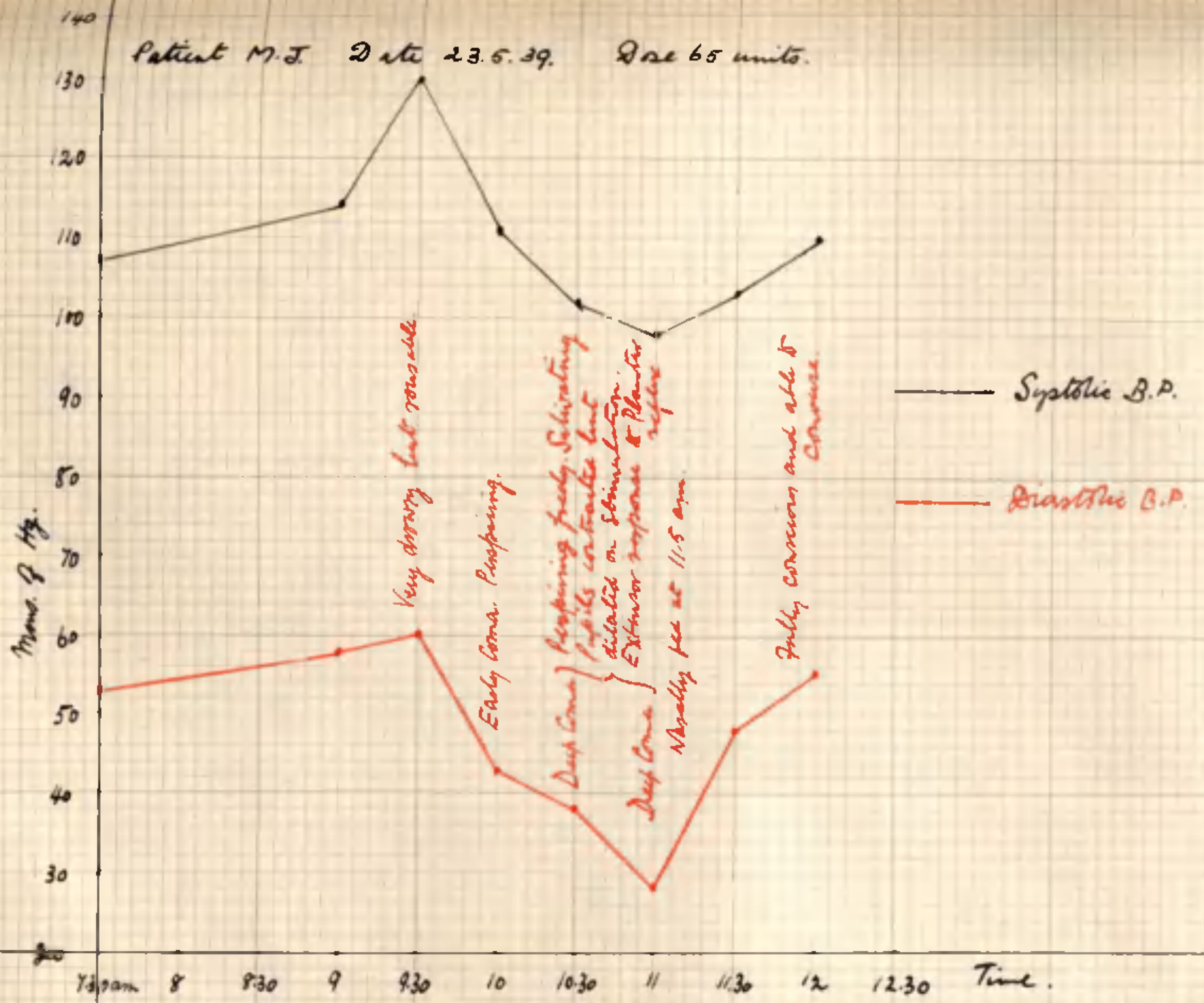

Patient M.J. Date 24.5.39. Dose 75 mils
Systolic B.P.
Diastolic B.P.
Mms. of Hg.
120
110
100
90
80
70
60
50
40
30
20
10
0
Very sweaty.
Early Coma.
Deep Coma. Perspiring very freely. Salivating. Pupils contracted.
Deep coma. Scarcely feel at 11.10 am.
Awoke and able to converse.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time

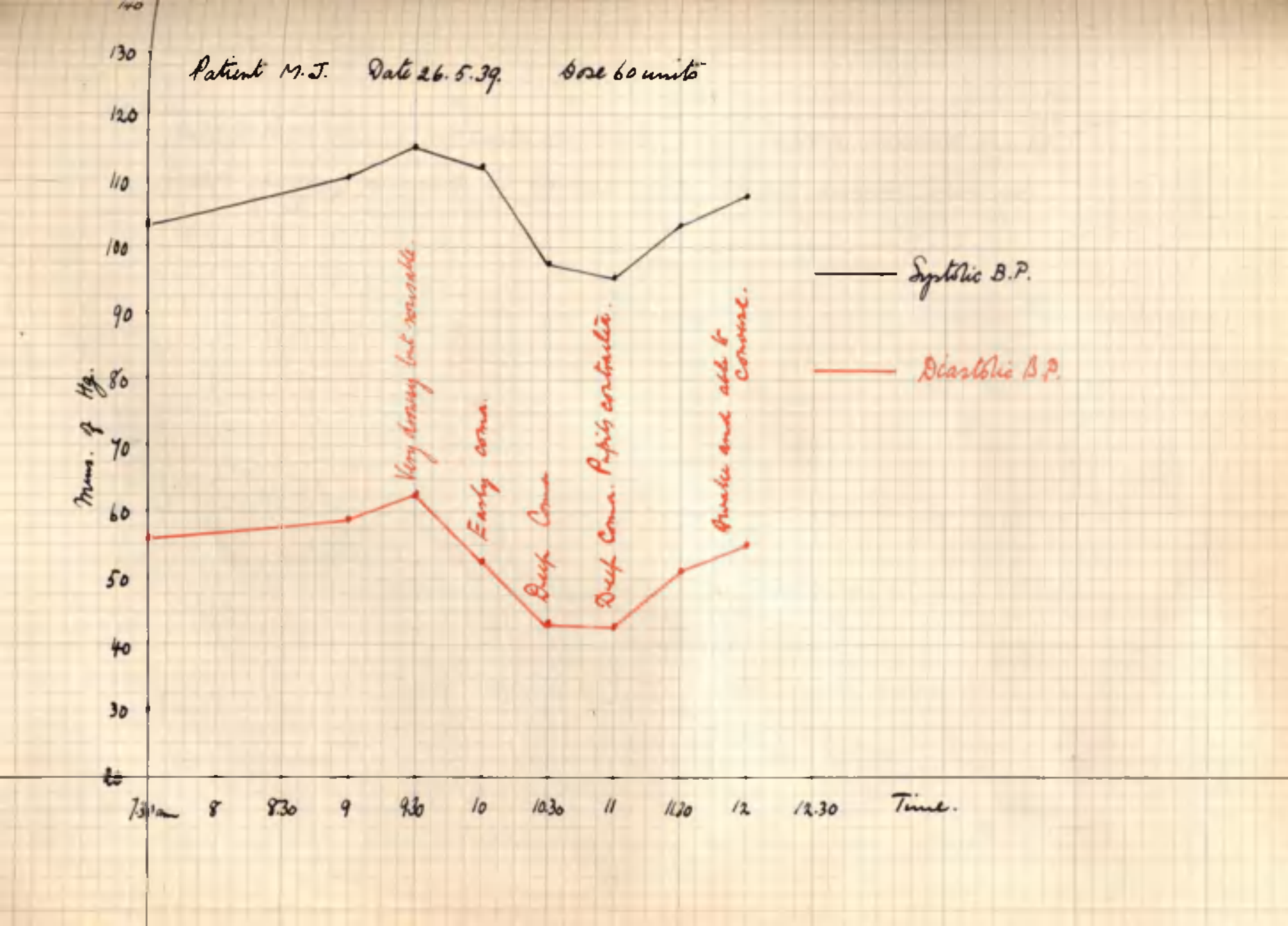

Patient M.J. Date 25.4.39. Dose 75 units.
140
130
120
110
100
90
80
70
60
50
40
30
20
mms. of Hg.
Very drowsy but rousable.
Early Coma. Respiring.
Deep Coma
Fair respiration
Profuse sweating
Deep Coma
Pupils contracted.
Normality has returned at 11.7 am.
Appears quite alert & conscious.
Systolic B.P.
Diastolic B.P.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30.
Time.


Patient M.J. Date 15.5.39. Dose 70 units.
Systolic B.P.
Diastolic B.P.
mms. of Hg.
120
110
100
90
80
70
60
50
40
30
20
10
0
Very drowsy.
Early coma. Perspiring.
Deep Coma.
Deep coma. Very fast respiration. Normality first at 11.5 am.
Awake and able to converse.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.

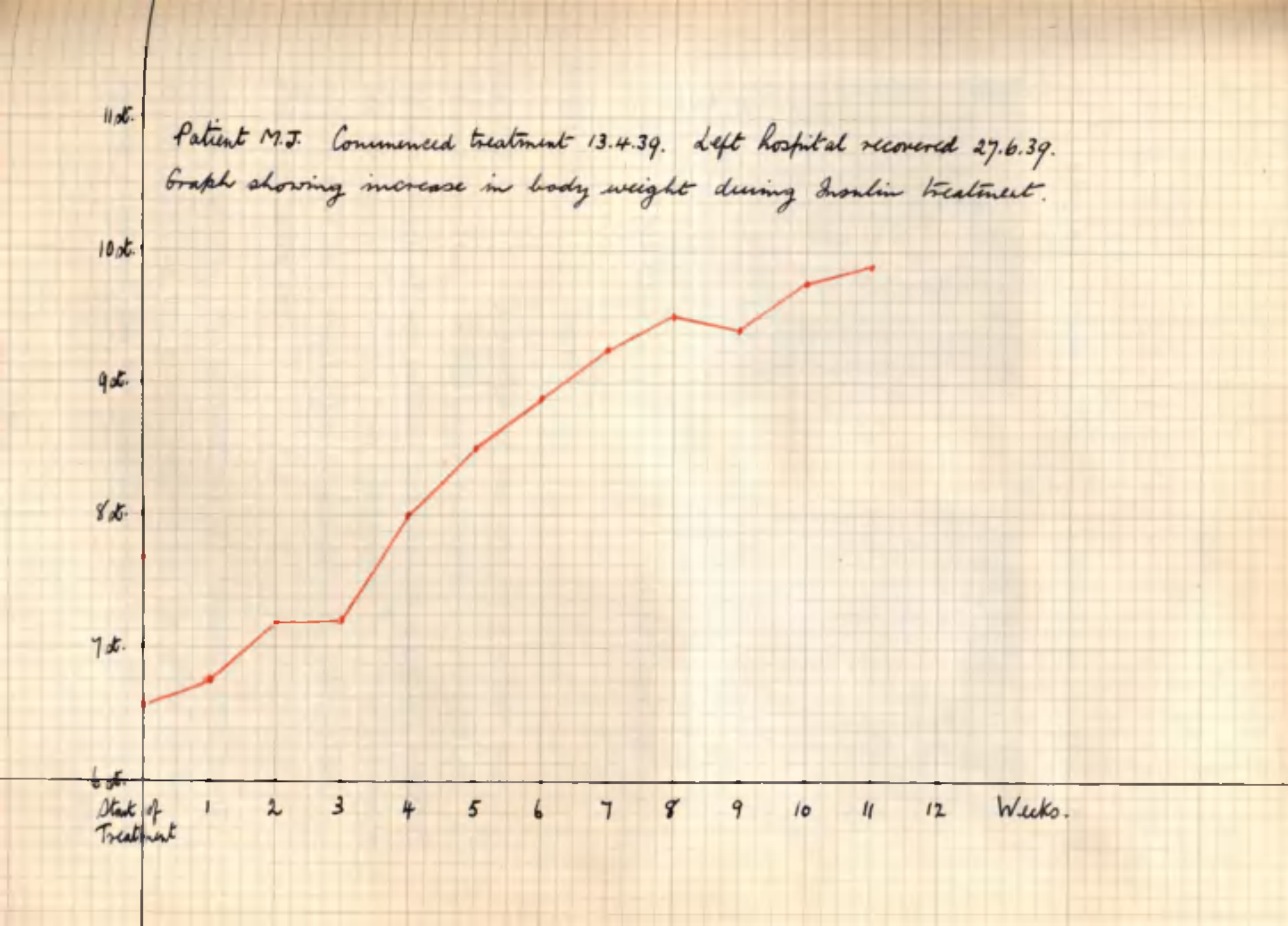

Patient M.J. Date 22.5.39. Dose 65 units
130
120
110
100
90
80
70
60
50
40
30
Mms. of Hg.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12.
12.30.
Time.
Systolic B.P.
Diastolic B.P.
Very drowsy. Perspiring
Early coma.
Deep Coma. Pupils contracted
Deep coma.
Normally fed at 11.10 am.
Fully conscious and able to converse.

Patient M.J. Date 23.5.39. Dose 65 units.




Patient M.J. Date 26.5.39. Dose 60 units
130
120
110
100
90
80
70
60
50
40
30
Mms. of Hg.
Very drowsy but responds.
Early coma.
Deep Coma
Deep Coma. Reflexes established.
Muscles and skin of
Systolic B.P.
Diastolic B.P.
7.30 a.m.
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.

Patient M.J. Commenced treatment 13.4.39. Left hospital recovered 27.6.39.
Graph showing increase in body weight during Isoniazid treatment.



C A S E 5.

D.J. Single. Aged 22 years. Admitted March 6th, 1939.

Before treatment.

After treatment.

OCCUPATION. Weaver.

HEREDITY. A sister of the patient's mother was in a mental hospital for six weeks following a confinement. A female cousin of the patient has been in a mental hospital for two years suffering from schizophrenia. The patient's mother died in a sanatorium from pulmonary tuberculosis fourteen years ago.

PERSONAL HISTORY. The patient was the youngest of a family of four, having two elder brothers and one elder sister. During childhood she suffered from measles, whooping cough and/

and scarlet fever. At the age of twelve she had rheumatic fever. She did well at school, reached the top form and was popular with the other children. After leaving school she went to work as a weaver, remained in the same job up to the time of her illness earning a salary of 17/- per week. In January 1938, she complained of being easily tired; her family doctor diagnosed Diabetes Mellitus for he discovered that she had glycosuria; she also lost a great deal of weight. She did not improve under treatment and in February 1938 was admitted to Manchester Royal Infirmary, various tests were performed there, she was rested in bed, not given any special diet, after two months she had improved greatly, she regained the weight she had lost and was discharged. The diagnosis was Hyper-thyroidism. For the rest of 1938 she kept in good health and was able to carry on at her work but in early February 1939 she again complained of not feeling well, she lost her appetite and refused to eat. On February 11th she had a violent emotional attack, cried for two hours and said that she needed an operation on her throat. As she absolutely refused all food and became violently excited and impulsive if food was brought to her, she was removed to the Municipal hospital on February 17th. She was transferred to Whittingham on March 6th, 1939.

PRE-PSYCHOTIC PERSONALITY. Her father described the patient as a good daughter, she got on well with her brothers and sister and was always bright and cheerful. At work she was highly regarded, she was attentive to her job and industrious.

On admission her bodily health was only moderate, she was thin and pale, her tongue was dry and furred, sordes were noticed around her teeth, her pulse was rapid 110, her throat was injected. Her thyroid gland appeared enlarged. Urine report was:- Sp. Gravity 1024, Acid, trace of albumen, trace of sugar, acetone present, the deposit showed a few pus cells and many epithelical cells. W.R. was negative and C.S.F. report was negative. Mentally she was dull, it was impossible to gain her attention and her talk was rambling and inconsequential. She was disorientated for time and place. She appeared to be hallucinated. Her habits were faulty and required to be spoonfed.

The following notes indicated her progress in hospital.

20th MARCH, 1939. "She still appears confused and answers questions irrelevantly, when asked how she was she replied "My mother's name is Mary Ann Dean". She displays no interest in her surroundings lying in bed staring into space."

27th MARCH, 1939. "She is very restless and excited today, she alternates crying and laughing and then bursts into song. She is often to be seen giggling and talking to herself."

28th MARCH, 1939. Urine Report. Sp. Gravity 1018, Acid. No albumen, no sugar and no acetone.

On April 2nd she was transferred to the insulin ward; in view of her history I was doubtful about giving her the treatment as both Hyperthyroidism and Diabetes Mellitus were amongst the contraindications to treatment. A blood sugar tolerance test was done, a graph is shown. There appeared to be a definite lag in getting back to the normal level, her urine was tested again and a trace of sugar was found. I decided to give her small doses of insulin to begin with and on April 5th she received 15 units of insulin and got the usual amount of glucose to follow, for the next three days she again had 15 units, she was then given 20 units for three days, 25 units for the next three, 30 units for the next three and on April 22nd she received 35 units. No ill effects were noticed, in fact the patient increased her weight by two pounds and instead of refusing her food ate readily. I now decided to push the dose up each day and on April 27th with a dose of 55 units she had her first coma; this was of the wet

type/

type and preceded by a restless period with some myoclonus. At this time apart from the fact that she ate better there was no mental improvement, her habits were faulty, she was very interfering and mischievous, stole other patients' belongings, broke cups and generally could not be trusted. She talked to herself a great deal and was often seen laughing and giggling to herself; when spoken to she did not answer; at times she showed impulsive tendencies, striking out viciously at the staff.

After four comas this patient showed the first sign of improvement, she asked for a hair brush and some hair clips and surprised everyone by appearing with her hair beautifully tidy, this was in direct contrast to her previous untidy appearance.

On May 10th 65 units were given at 7.30 a.m. Up to 9.45 a.m. she lay quietly in bed in a drowsy state, but she then began to become restless and noisy, she threw her arms about and rolled about the bed, she was removed onto the floor mattresses and allowed to fling herself about. Her pupils could be seen to be dilated, she was perspiring. By 10.15 a.m. the restlessness was passing off and coma developed, the pupils became contracted, perspiration was profuse; at 10.35a.m. she was judged to be in deep coma, increased salivation had

become/

become very evident. At 10.45 a.m. it was noticed that her pulse was irregular in rhythm and she was nasally fed immediately, by 11.15 a.m. she was quite conscious, had eaten her portion of cake and was ready to converse. What happened upon that day was not usual for this patient, her restless phase was not usually so severe. I felt that the cardiac irregularity was probably due to the earlier severe restlessness.

On May 16th a mental note read "This patient is improving, her behaviour is good, she is clean and tidy and takes a real pride in her appearance. She occupies herself in the ward usefully and is showing plenty of initiative; questioned about her illness she realises she has been mentally ill and is keen to get better and go home."

Throughout her treatment this patient had a morning (before treatment) and afternoon specimen of urine tested each day. On practically every day there was sugar in both specimens, although a greater amount in the afternoon specimen. She was never given any special diet and received exactly the same food as the other patients. A careful watch was kept on her weight, a graph of which was made.

On May 27th she was given 40 units at 7.30 a.m., the dose had been dropped because the patient was developing a sensitivity to insulin. She was drowsy and quiet up to 9.55 a.m. when some facial myoclonus was noticed, this was almost immediately followed by a severe fit, she was nasally fed with glucose at 10.5 a.m. and was coming round at 10.30 a.m.

After this point her dose was gradually cut down, she had her last coma on June 9th and treatment was concluded on June 12th. In all she had thirty seven comas. This patient never complained about the treatment, she soon came to realise that it was helping her, occasionally she dreamt and most of her dreams were concerned with food. Following the conclusion of her treatment her urine was examined daily and a blood sugar tolerance test was performed, a graph of this is shown. She was kept on a perfectly normal diet, an occasional trace of sugar was found in her urine.

The patient was discharged on July 1st, 1939.

OBSERVATIONS ON PUPIL CHANGES DURING HYPOGLYCAEMIA.

(1) 3.5.39.	TIME.	SIZE.	OBSERVATIONS.
	7.30 a.m.	7 mms.	
	9 a.m.	6.5 mms.	Drowsy and quiet.
	9.30 a.m.	5.5 mms.	Drowsy and quiet, some perspiration.
	10.5 a.m.	8 mms.	Restless - Myoclonus. Dilated pupils. Contracted pupils.
	10.22 a.m.	5 mms.	Quiet interval during the restlessness.
	11 a.m.	3 mms.	Deep coma, perspiring freely, salivating. Slow pulse 63. Stimulation of the patient led to a dilatation of the
	11.30 a.m.	3 mms.	pupils after a latent period of 1-2 secs. This dilatation disappeared in 15 secs. if the patient was left quiet. At the same time the pulse rate quickened and then slowed.
	12.10 p.m.	6.5 mms.	Awake after nasal feeding.

(2) 8.5.39.	TIME.	SIZE.	OBSERVATIONS.
	7.30 a.m.	7 mms.	
	9.5 a.m.	7 mms.	
	9.40 a.m.	5.5 mms.	Drowsy and quiet.
	10.0 a.m.	7.5 mms.	Restlessness with myoclonus, perspiring.

(2) contd.

TIME.	SIZE.	OBSERVATIONS.
10.30 a.m.	4 mms.	Early coma, perspiring.
11.0 a.m.	3.5 mms.	Deep coma, perspiring and salivating.
11.45 a.m.	7 mms.	Awake after nasal feeding.

(3) 11.5.39.

TIME.	SIZE.	OBSERVATIONS.
9 a.m.	6 mms.	
9.30 a.m.	6 mms.	Drowsy and quiet.
9.55 a.m.	8 mms.	Restlessness with myoclonus.
10.12 a.m.	4.5 mms.	Quiet interval during the restless period.
10.20 a.m.	7.5 mms.	Restlessness. Pupils dilated.
10.35 a.m.	4 mms.	Early coma.
11.10 a.m.	3 mms.	Deep coma.
12 noon	7 mms.	Awake after nasal feed.

(4) 19.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9 a.m.	6.5 mms.	
9.35 a.m.	7.5 mms.	Commencing to be restless.
9.45 a.m.	5 mms.	Quiet interval during the restless period.
9.50 a.m.	7 mms.	Restless myoclonic phase.
10.15 a.m.	4.5 mms.	Coma, perspiring.

(4) contd.

TIME.	SIZE.	OBSERVATIONS.
11.0 a.m.	3 mms.	Deep coma, perspiring freely, salivating. Slow pulse 60. A slight stimulation made the pupils dilate up to 8 mms. after a latent interval of 1-2 secs. The dilatation passed off in 15 secs. Accompanying the pupil dilatation was a quickening of the pulse.
12.0 noon	7 mms.	Awake after nasal feed.

(5) 24.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.0 a.m.	7 mms.	Drowsy and quiet.
9.30 a.m.	8 mms.	Restlessness with myoclonus.
10.0 a.m.	4 mms.	Early coma, perspiring.
10.30 a.m.	3 mms.	Deep coma, perspiring freely, salivating.
10.50 a.m.	3 mms.	Slow pulse 66.
11.25 a.m.	6.5 mms.	Awake after nasal feed.

(6) 25.5.39.

TIME.	SIZE.	OBSERVATIONS.
9.0 a.m.	6.5 mms.	
9.25 a.m.	7 mms.	Commencing restlessness.
9.43 a.m.	5 mms.	Quiet interval during the restless phase.
10.0 a.m.	8 mms.	Very restless. Myoclonus. Pupils dilated.
10.25 a.m.	5 mms.	Early coma, perspiring.
11.0 a.m.	3 mms.	Deep coma, perspiring freely, salivating profusely. Slow pulse 66.
11.30 a.m.	3 mms.	
12.15 p.m.	6 mms.	Awake after nasal feed.

(7) 26.5.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9.5 a.m.	7 mms.	Drowsy and quiet.
9.30 a.m.	8 mms.	Restless.
9.42 a.m.	5.5 mms.	Quiet interval during restless phase.
9.58 a.m.	8 mms.	Restless again.
10.30 a.m.	3.5 mms.	Deep coma. Perspiring and salivating. Slow pulse 70. Pupils dilated when the patient was disturbed but rapidly changed back to the contracted state when the patient was left alone.
11.0 a.m.	3 mms.	
11.50 a.m.	6.5 mms.	Awake after nasal feed.

(8) 31.5.39.

TIME.	SIZE.	OBSERVATIONS.
9 a.m.	6.5 mms.	
9.30 a.m.	6 mms.	Drowsy and quiet.
9.50 a.m.	8 mms.	Restlessness.
10.2 a.m.	6 mms.	Quiet interval during the restless stage.
10.10 a.m.	8 mms.	Restlessness again.
10.30 a.m.	4.5 mms.	Early coma.
11.0 a.m.	3 mms.	Deep coma, perspiring, salivating.
11.25 a.m.	3 mms.	Slow pulse 58.
12.5 p.m.	7 mms.	Awake after nasal feed.

(9) 1.6.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7.5 mms.	
10.20 a.m.	5.5 mms.	Early coma, perspiring.
11.15 a.m.	3 mms.	Deep coma.
12.10 p.m.	6.5 mms.	Awake after nasal feed.

(10) 2.6.39.

TIME.	SIZE.	OBSERVATIONS.
9 a.m.	6 mms.	Drowsy and quiet.
10 a.m.	7.5 mms.	Restless. Pupils dilated.
11.5 a.m.	3 mms.	Deep coma. Pupils contracted.
12 noon	7 mms.	Awake after nasal feed.

(11) 3.6.39.

TIME.	SIZE.	OBSERVATIONS.
7.30 a.m.	7 mms.	
9 a.m.	6.5 mms.	
9.30 a.m.	6.0 mms.	Drowsy and quiet.
9.55 a.m.	8 mms.	Restless.
10.3 a.m.	5 mms.	Quiet interval during restless stage.
10.15 a.m.	8 mms.	Restless again.
10.30 a.m.	4.5 mms.	Early coma. Perspiring.
10.55 a.m.	3 mms.	Deep coma, perspiring, salivating. Slow pulse 60. Gentle stimulation of the patient produced a dilatation of the pupils after a latent period of 1-2 secs. When left alone the pupils contracted again after about 15-20 secs.
11.20 a.m.	3 mms.	
12 noon	7 mms.	Awake after nasal feeding.

(12) 5.6.39.

TIME.	SIZE.	OBSERVATIONS.
9 a.m.	6.5 mms.	
9.35 a.m.	7 mms.	
10 a.m.	8 mms.	Restlessness.
10.15 a.m.	8 mms.	Restlessness. Perspiring.
10.30 a.m.	4.5 mms.	Early coma. Perspiring.
11.0 a.m.	3 mms.	Deep coma. Pupils contracted.
11.25 a.m.	3 mms.	
12.5 p.m.	7 mms.	Awake after nasal feeding.

In this patient, during the first quiet stage the pupils became slightly smaller, following this was the restless myoclonic stage during which the pupils were dilated; if, however, a lull occurred in this restless stage the pupils were found to have contracted. After the restless stage came the coma during which the pupils became progressively smaller, a stimulation of the patient though produced a temporary dilatation of the pupils lasting 15-20 secs. and coming on after a latent period of 1-2 secs. Following the nasal feed the pupils returned to their normal size.

BLOOD SUGAR OBSERVATIONS.

Two blood sugar tolerance tests, one before treatment and one after, and five blood sugar curves following insulin are shown.

After treatment there appeared to be a greater tendency for the blood sugar to return to normal, although after one and a half hours the blood sugar level was higher than normal. As usual the greatest fall in the blood sugar occurred in the first one and a half to two hours when apart from drowsiness there were no symptoms. The coma level appeared to be from 25 mgms. per 100 ccs to 38 mgms. per 100 ccs.

In several of the graphs, the lowest blood sugar level was during the restless stage and following this stage there was a slight rise and in two cases followed again by a drop as coma came on and became deeper. This patient, like others, was fully conscious and yet the blood sugar level was not as high as it was before the morning's treatment commenced. A definite sensitivity to insulin developed as treatment progressed and a dose of 35 units on June 6th produced just as great a fall of blood sugar as a dose of 60 units on April 29th.

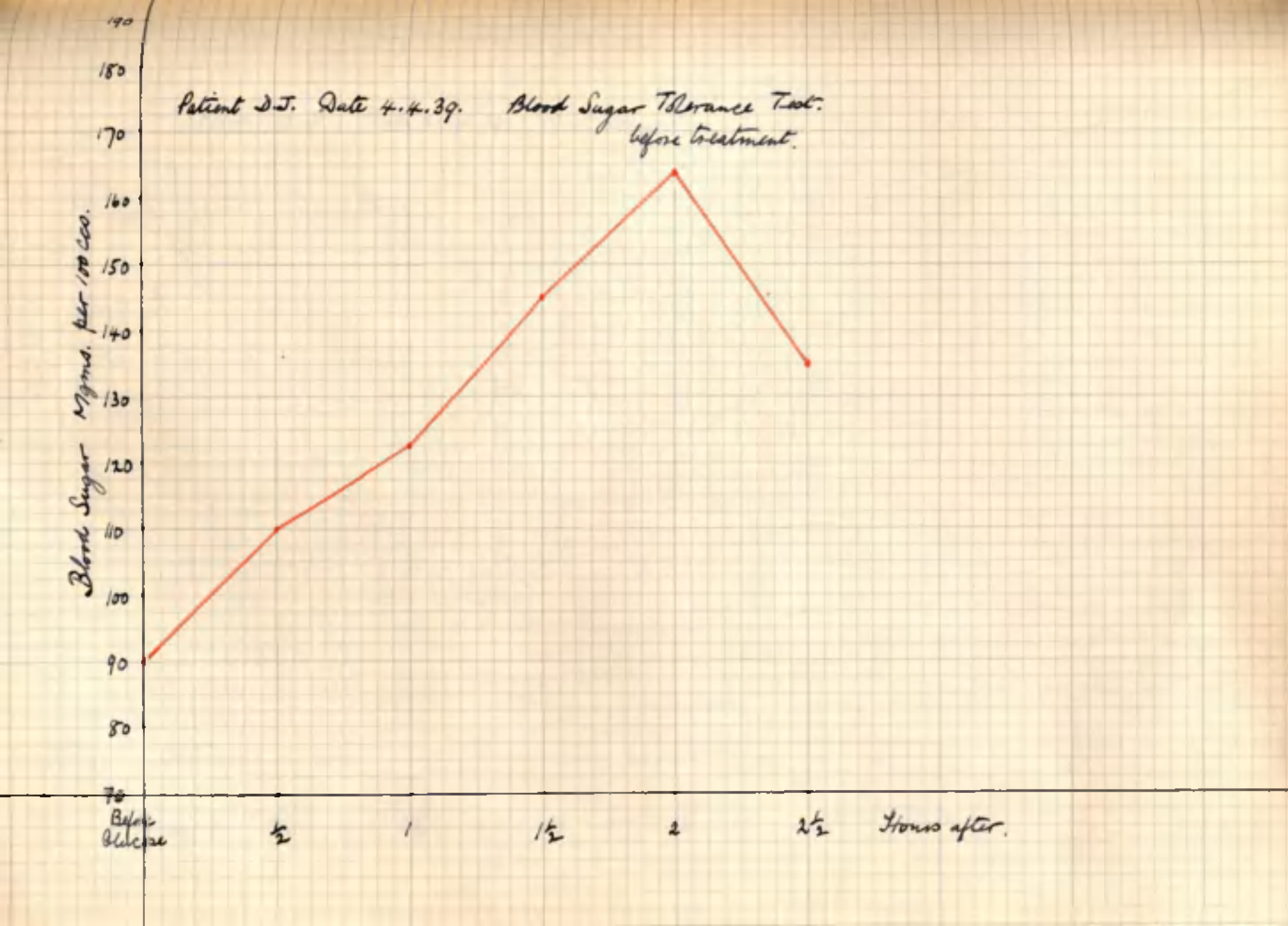
PULSE RATE OBSERVATIONS.

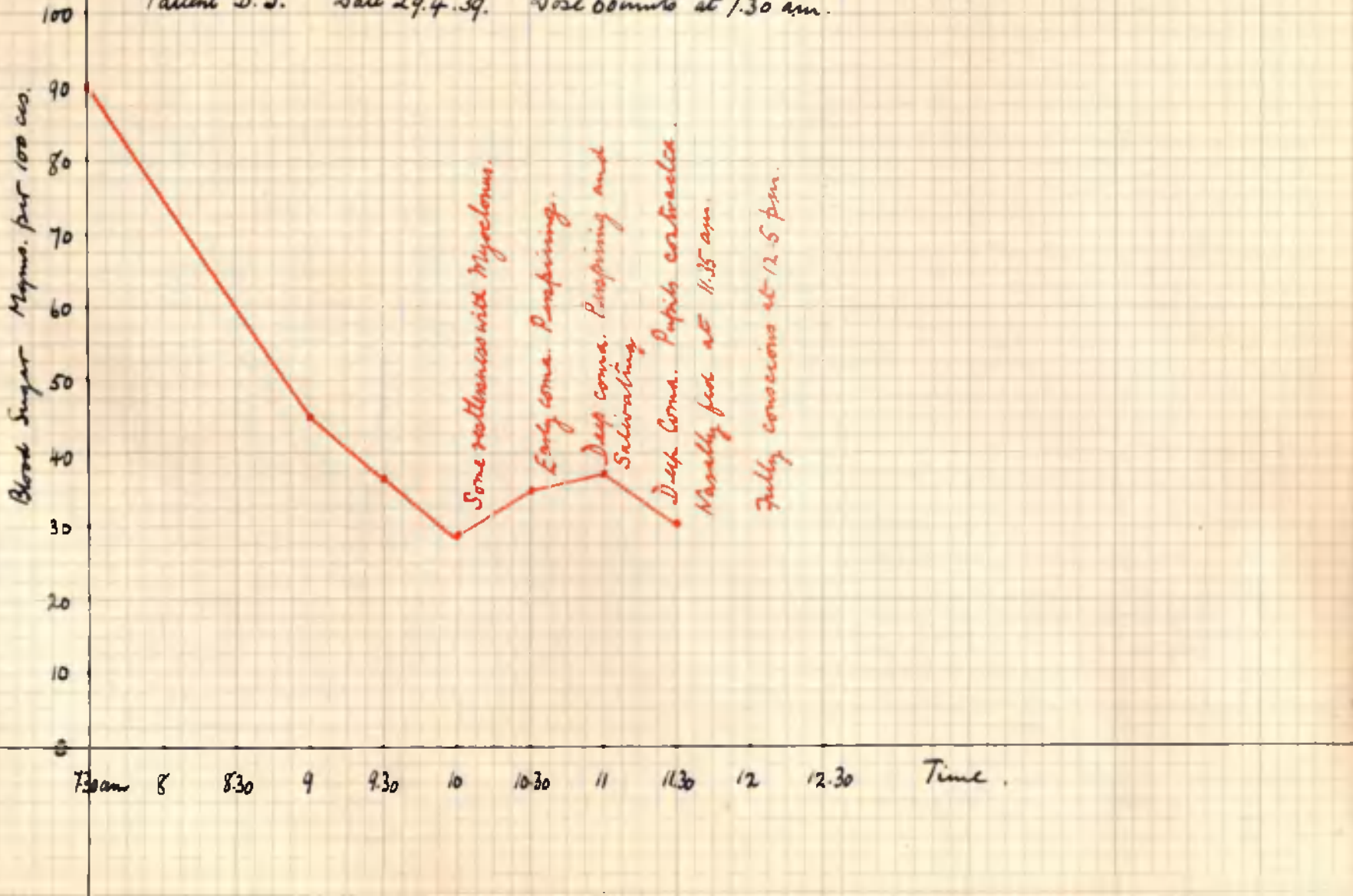
Nine of the daily pulse charts are shown. The initial tachycardia was noted and concurrent with this was the restless myoclonic period. On May 10th when the patient was very restless, the pulse rate almost reached 120, on the other days when the restlessness was not so marked, the tachycardia was also not so marked. Similar to the other patients when once coma started the pulse rate slowed although stimulation of the patient brought about a short temporary quickening, this however soon disappeared when the patient was left quiet.

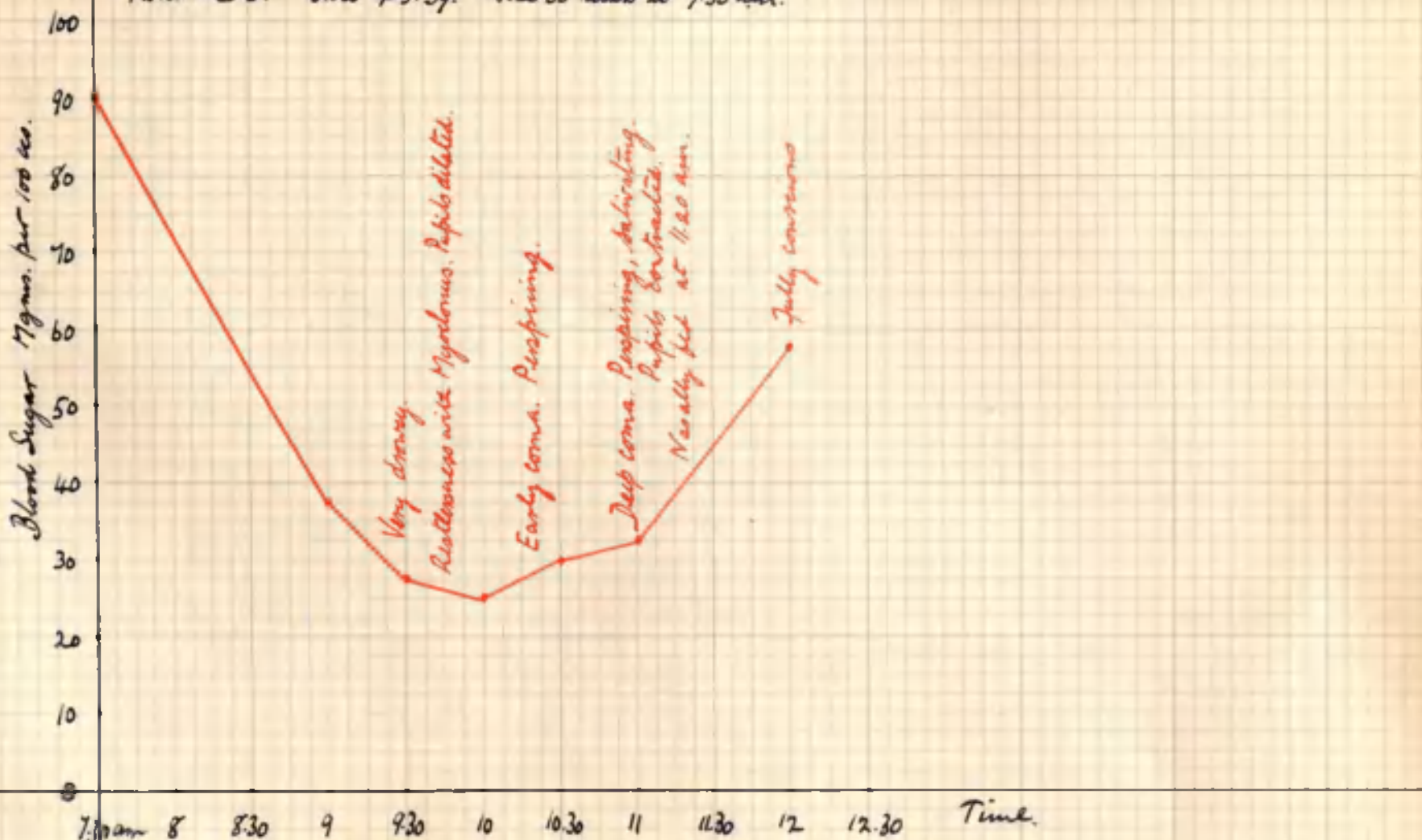
BLOOD PRESSURE OBSERVATIONS.

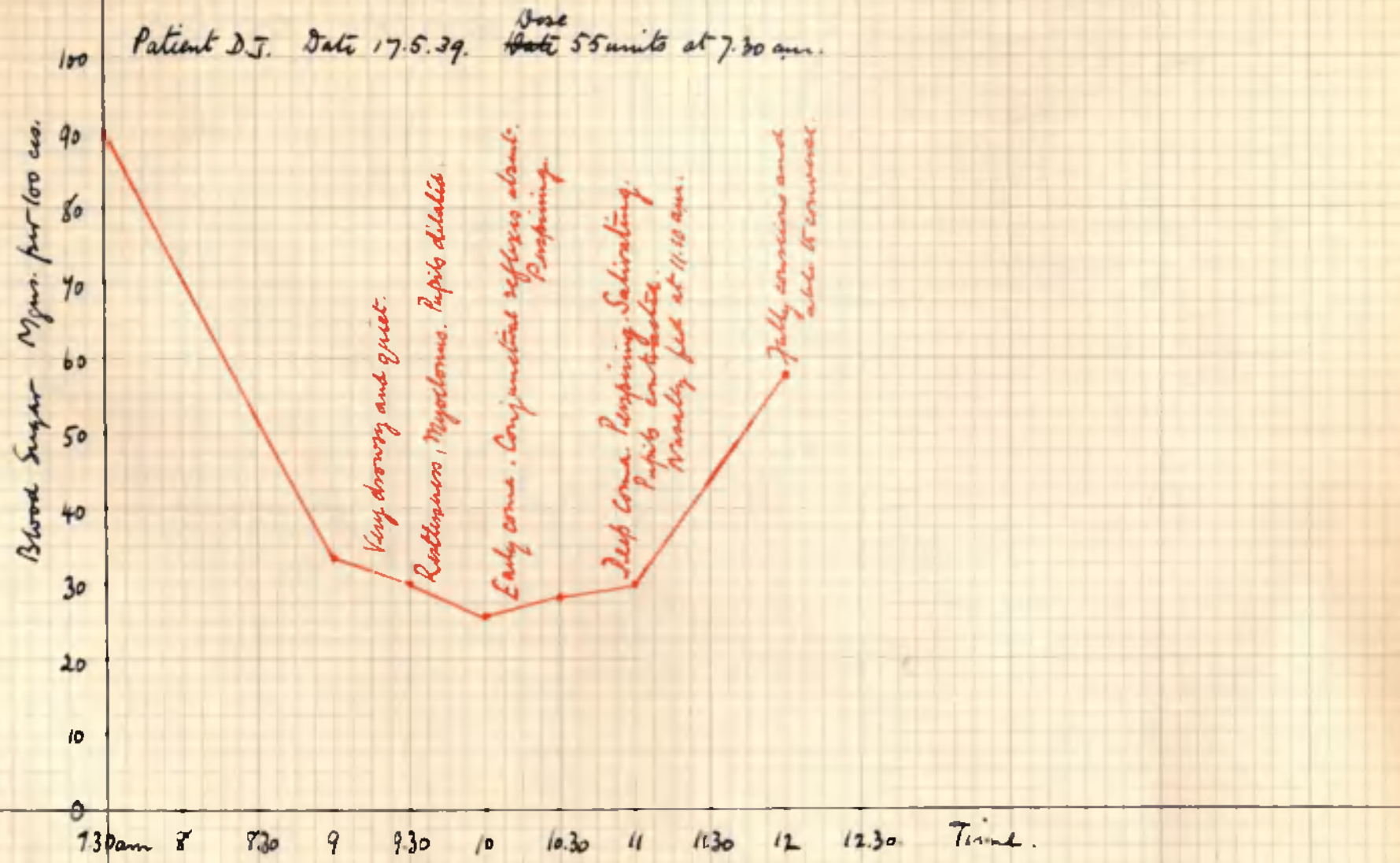
Five graphs of the systolic and diastolic pressures following the injection of insulin are shown. A rise in both systolic and diastolic pressures took place in the early restless stage being more marked in the systolic. As coma developed both pressures fell, the fall in the diastolic being more marked. The pulse pressure was thus increased. After nasal feeding there was an approximation of both pressures towards the normal pressure.

The weekly weight graph in this patient showed a definite upward curve.

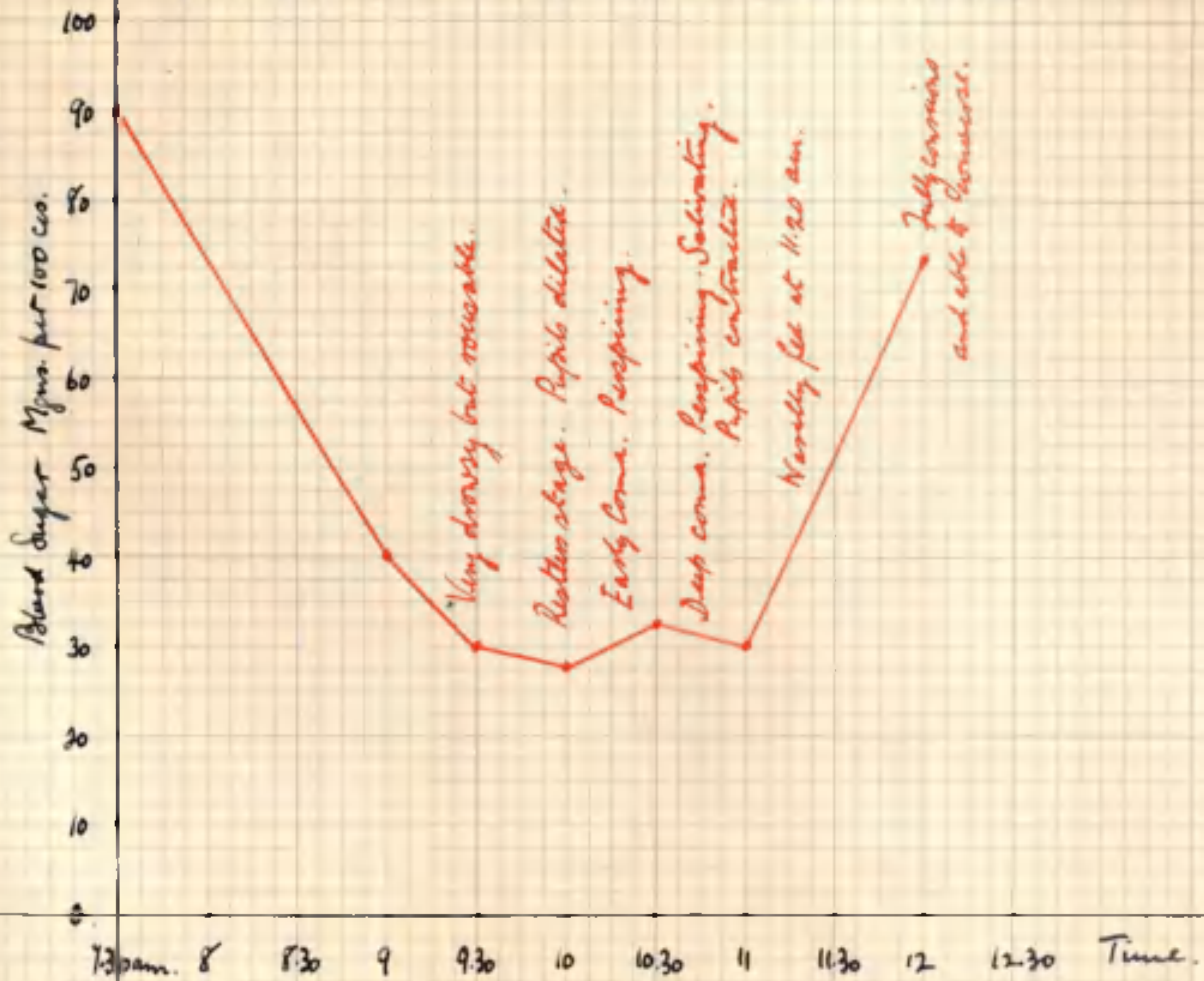

Patient D.J. Date 4.4.39. Blood Sugar Tolerance Test.
before treatment.
Blood Sugar Mgms. per 100 cco.
190
180
170
160
150
140
130
120
110
100
90
80
70
Before Breakfast
½
1
1½
2
2½
Hours after.


Patient D. J. Date 29.4.39. Dose 60 units at 7.30 am.
Blood Sugar Mgms. per 100 cc.
100
90
80
70
60
50
40
30
20
10
0
Some restlessness with Myoclonus.
Early coma. Perspiring.
Deep coma. Perspiring and Salivating
Deep Coma. Pupils contracted.
Normality first at 11.35 am.
Fully conscious at 12.5 pm.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.

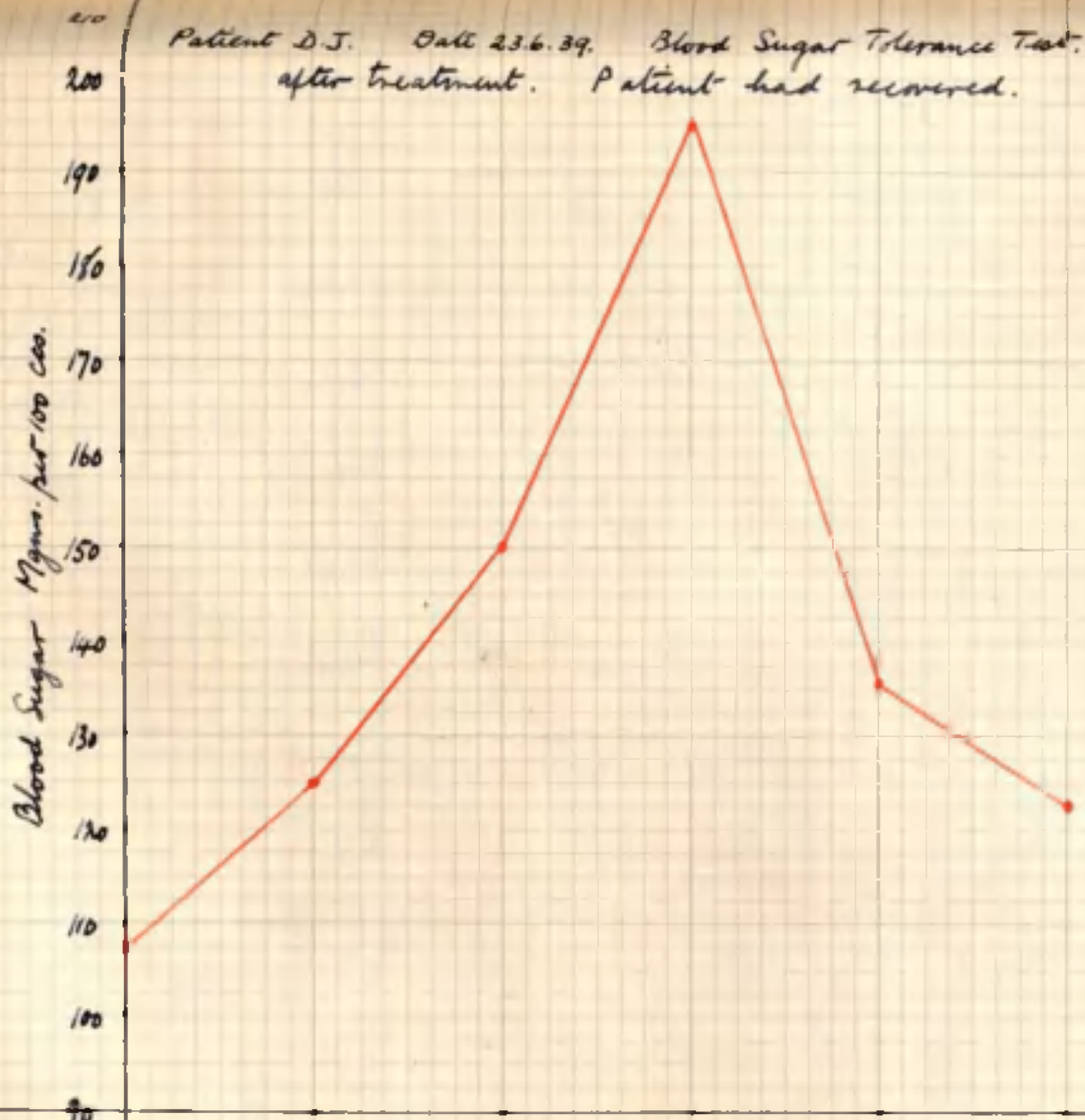

Patient D.J. Date 4.5.39. Dose 60 units at 7.30 am.
Blood Sugar Mgms. per 100 cc.
100
90
80
70
60
50
40
30
20
10
0
Very drowsy.
Restlessness with Myoclonus. Pupils dilated.
Early coma. Perspiring.
Deep coma. Perspiring, salivating. Pupils contracted. Nearly fed at 11.20 am.
Fully conscious
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.


Patient D.J. Date 17.5.39. Dose 55 units at 7.30 am.
Blood Sugar Mgms. per 100 ccs.
100
90
80
70
60
50
40
30
20
10
0
Very drowsy and quiet.
Restlessness, Myoclonus. Pupils dilated
Early conv. Conjunctival reflexes absent. Perspiring.
Deep conv. Perspiring. Salivating. Pupils contracted. Normality first at 11.10 am.
Fully conscious and able to converse.
7.30am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.

Patient D.J.   Date 6.6.39.   Dose 35 units at 7.30 am.



Patient D.J. Oakl 23.6.39. Blood Sugar Tolerance Test.
after treatment. Patient had recovered.



4 HOUR CHART.

DISEASE

Name { D. J.

Age

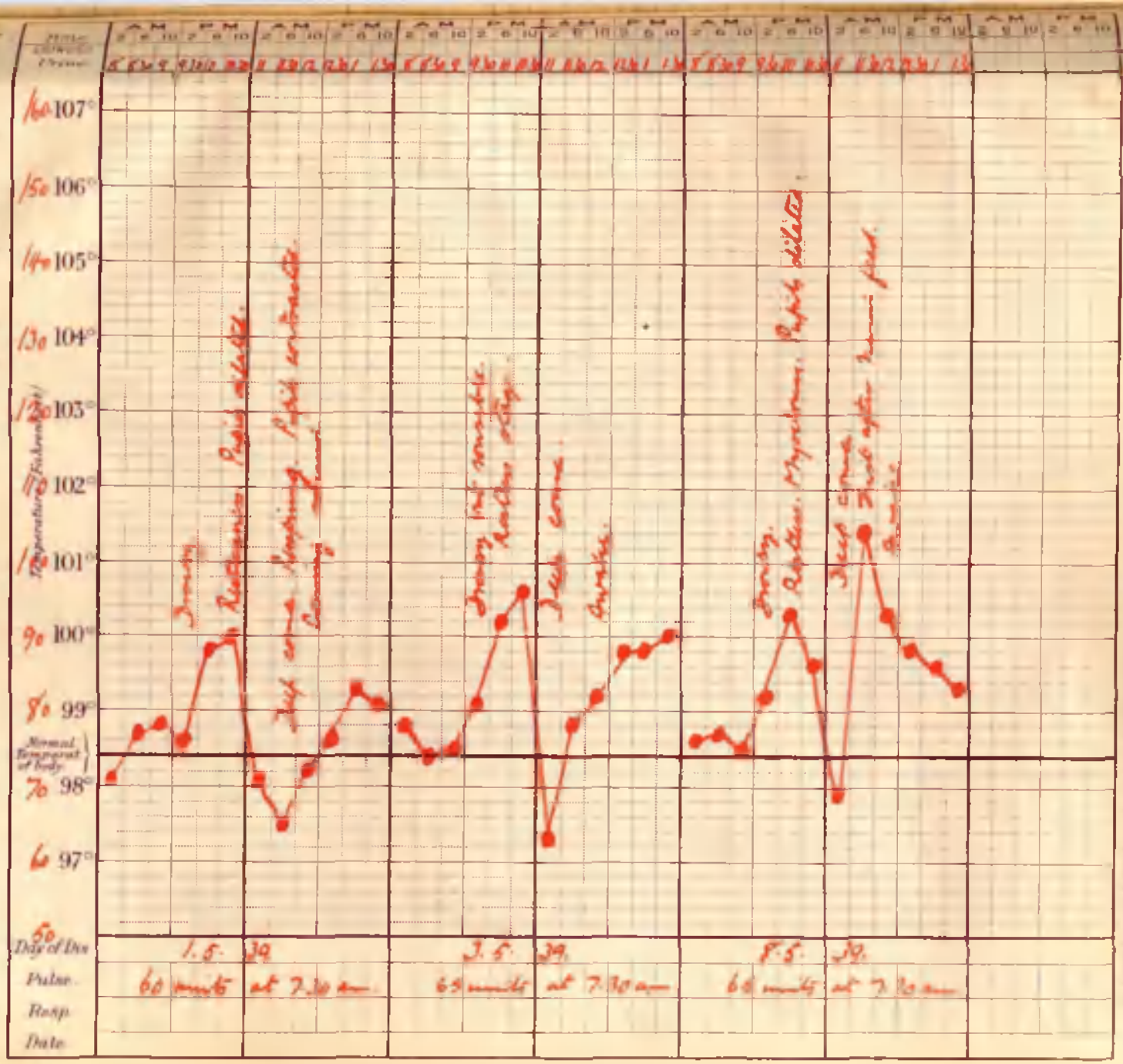
Diet

Case Book N°

Notes of Case

Date of admission

Result



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Gould's Clinical Chart

4 HOUR CHART

DISEASE

Name D.J.

Age

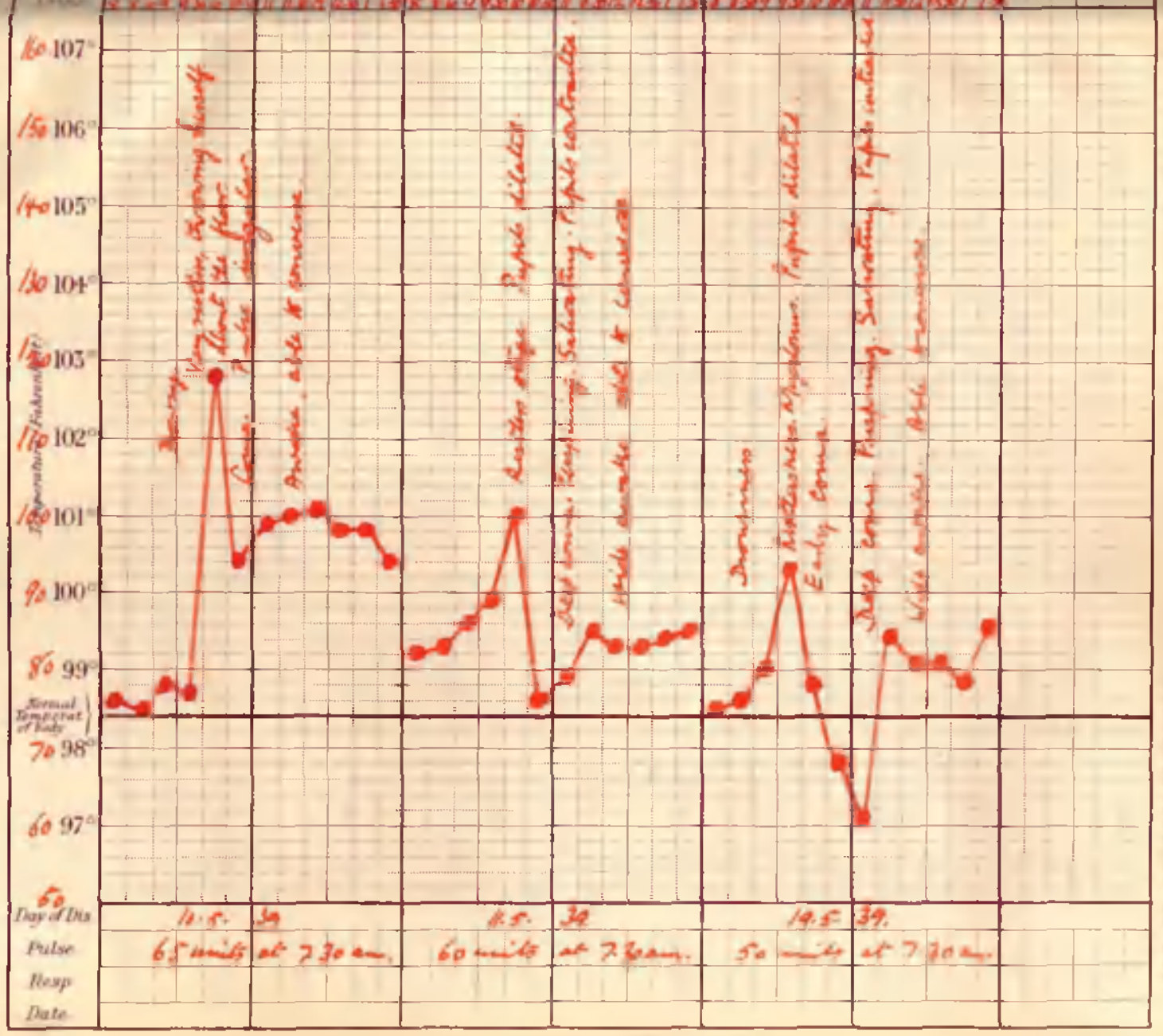
Diet

Case Book N°

Notes of Case

Date of admission

Result



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Goulds Clinical Chart

4 HOUR CHART.

DISEASE

Name D. J.

Age

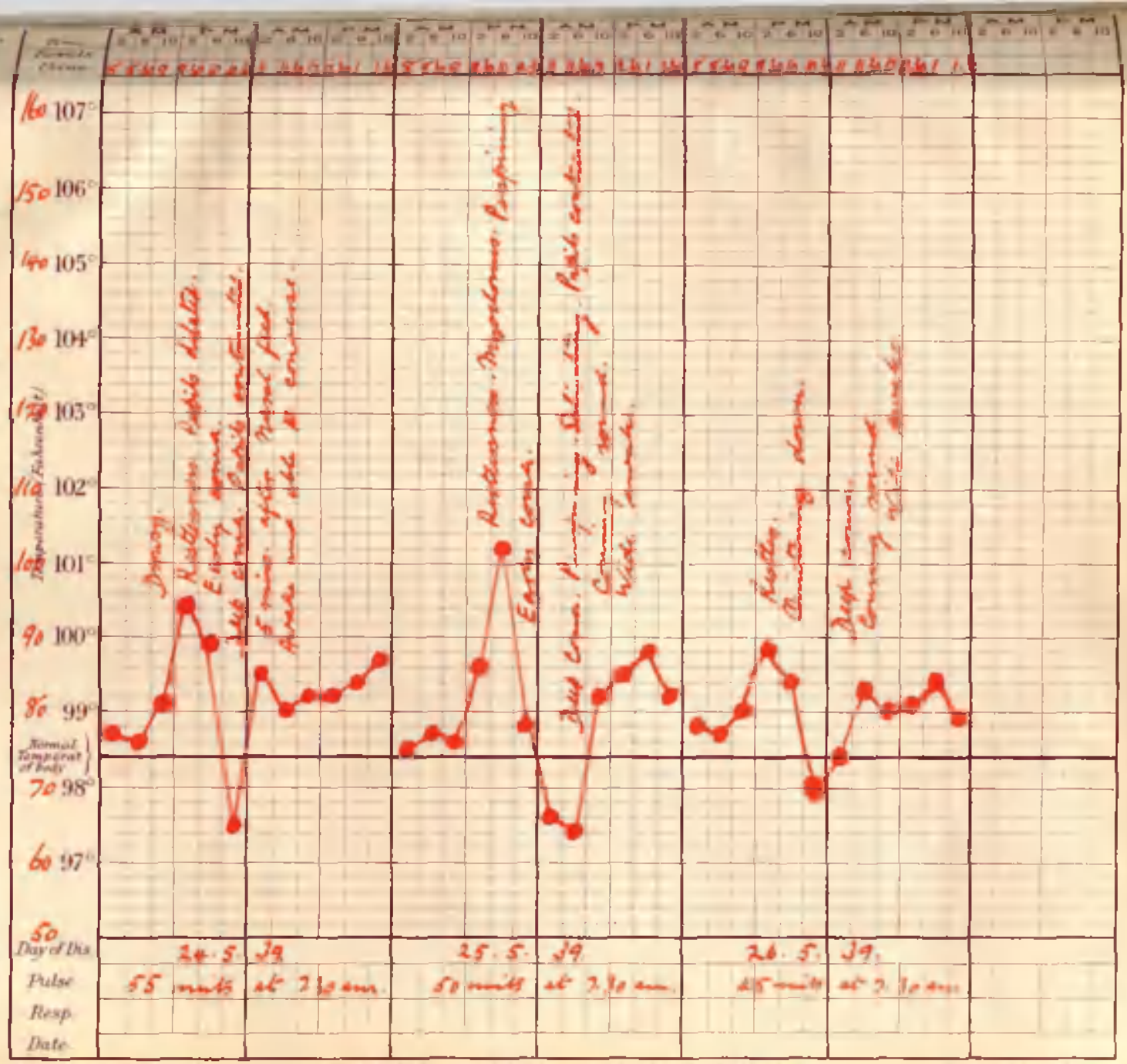
Diet

Case Book N°

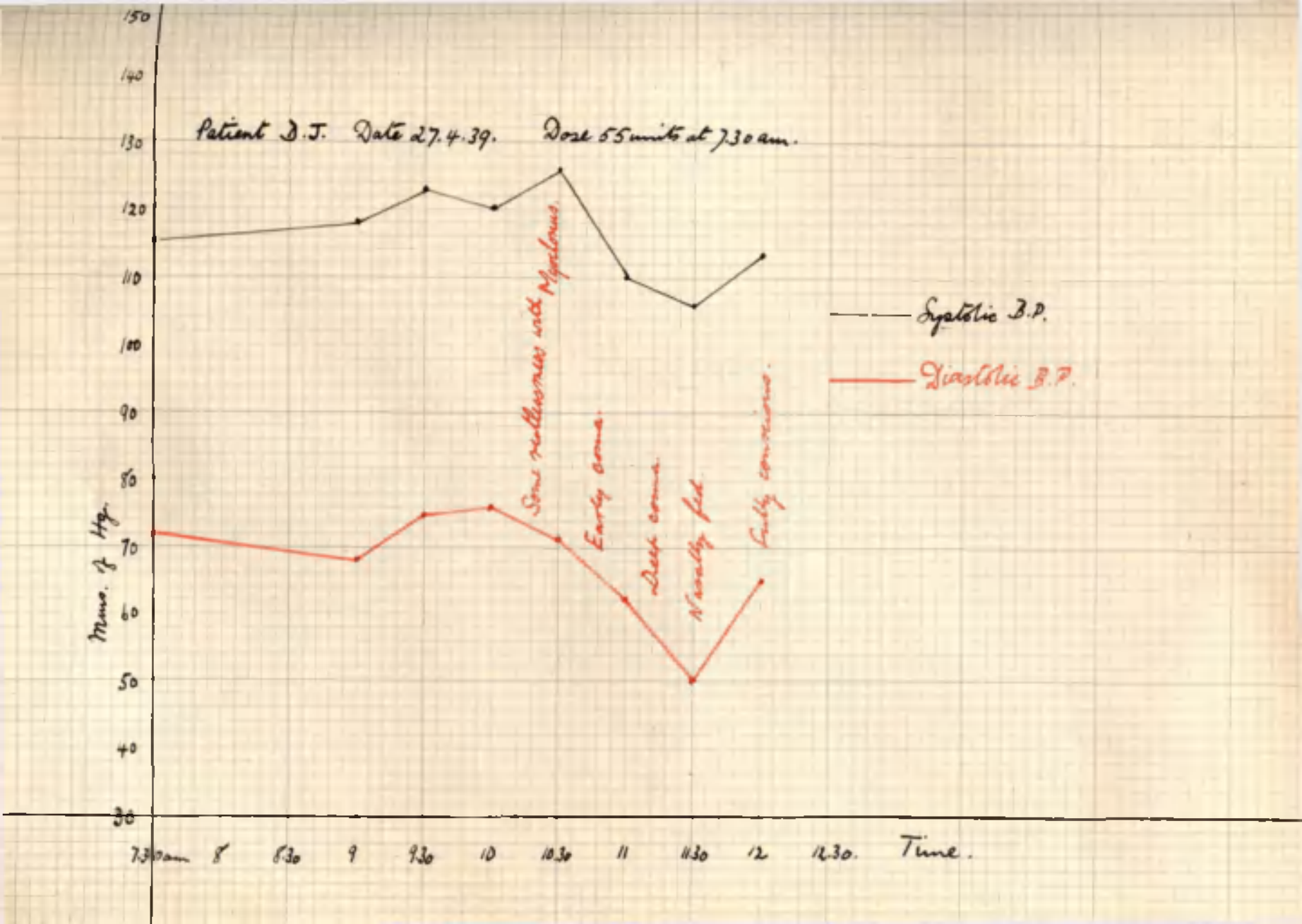
Notes of Case

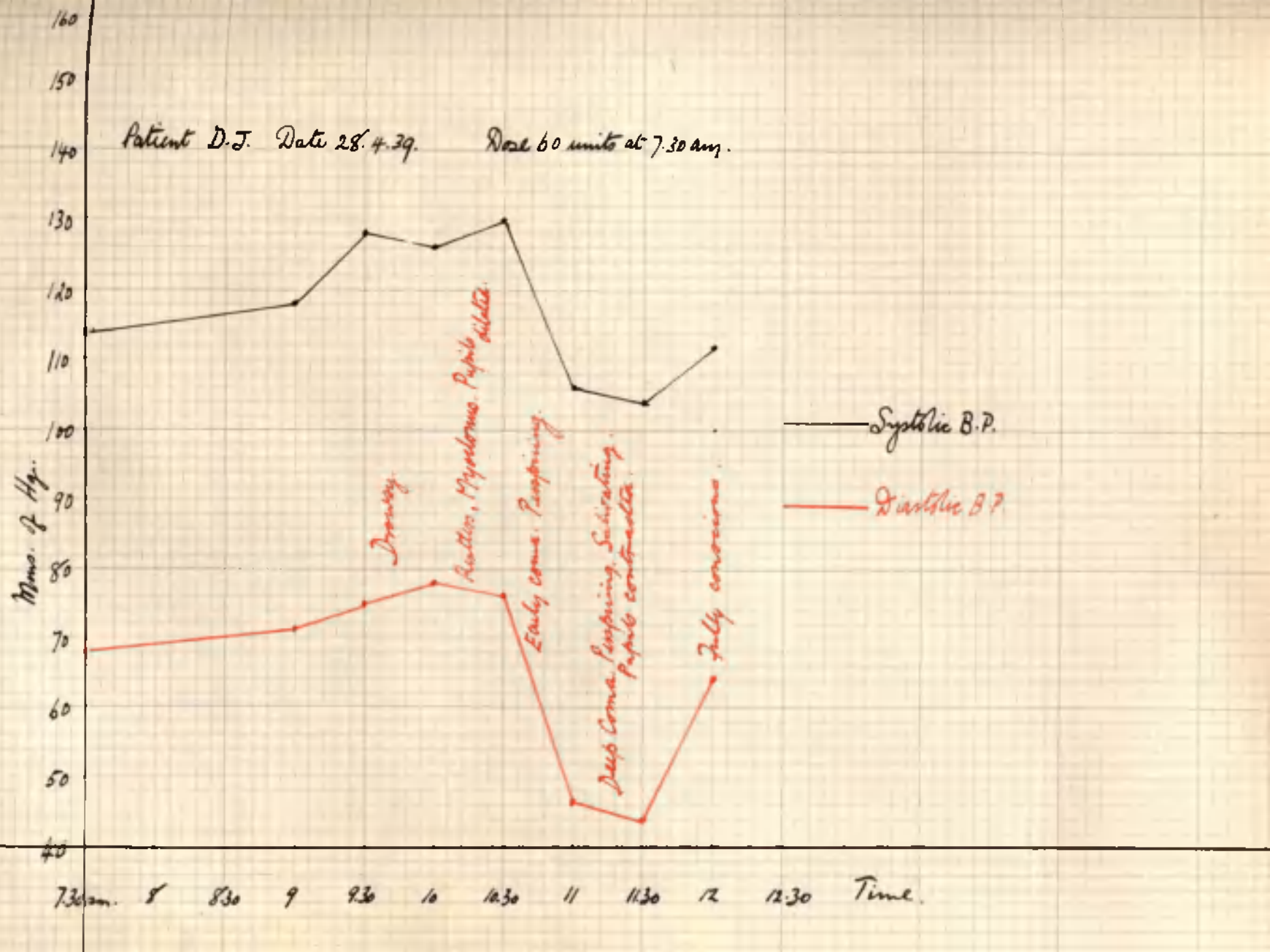
Date of admission

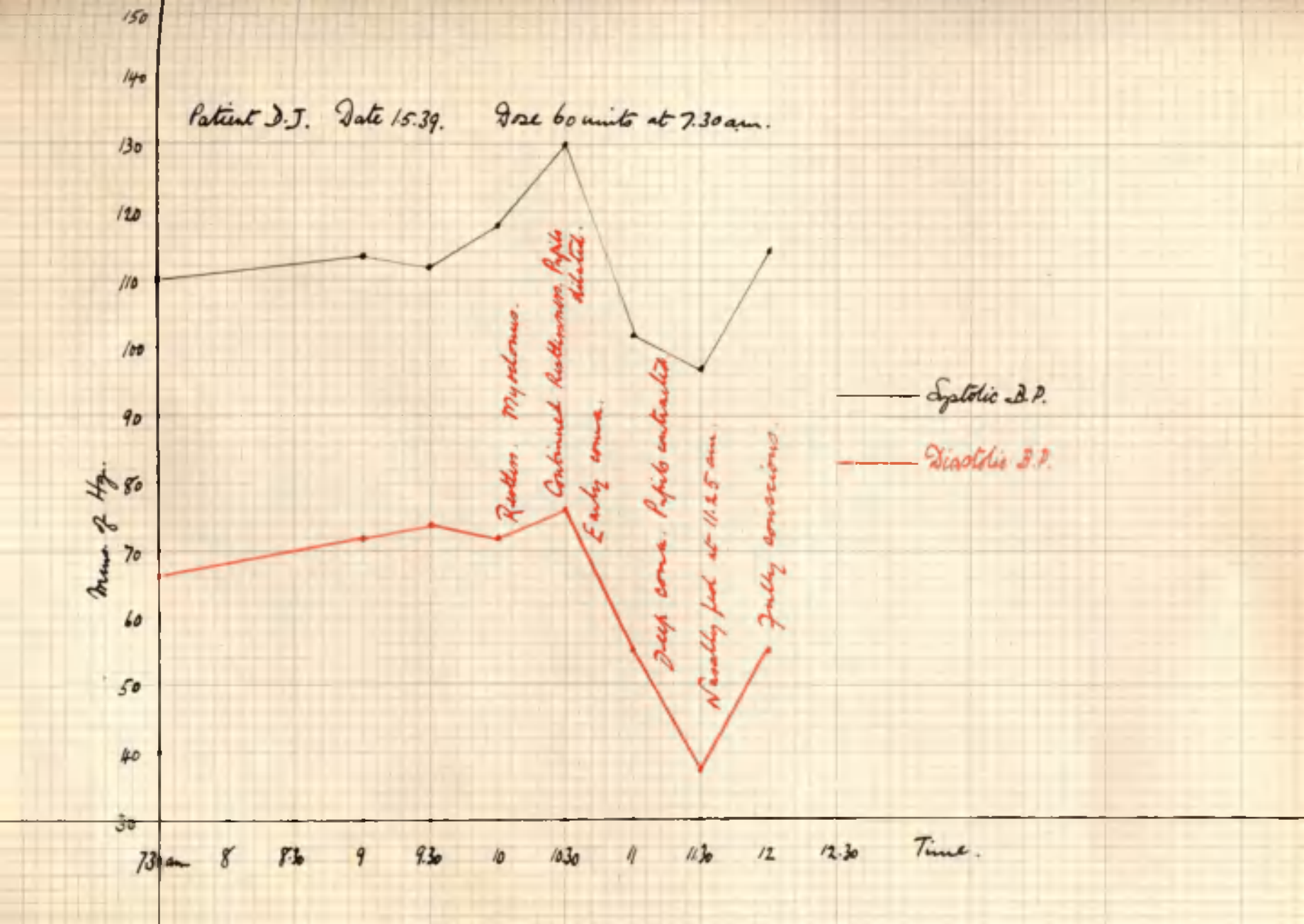
Result

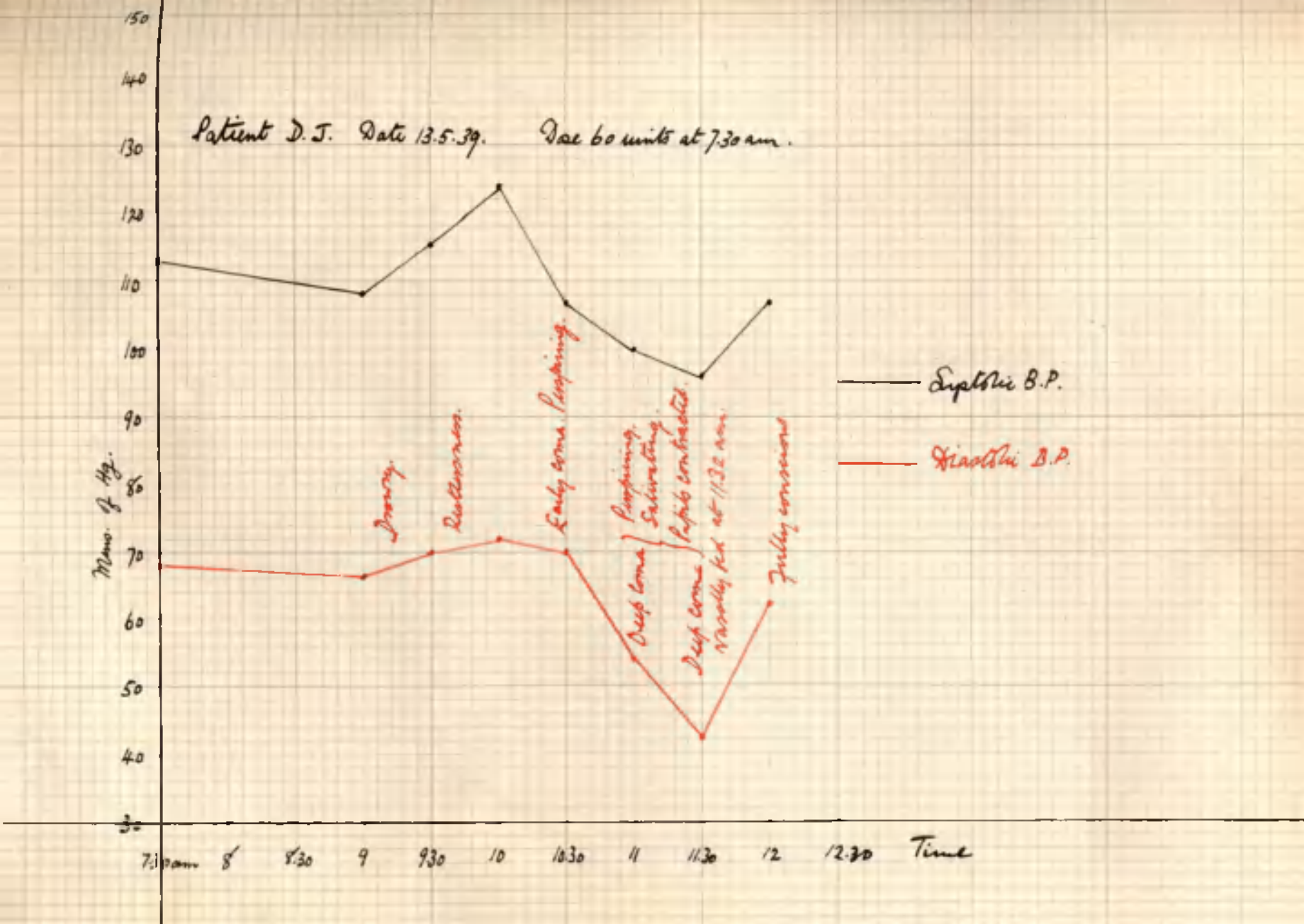


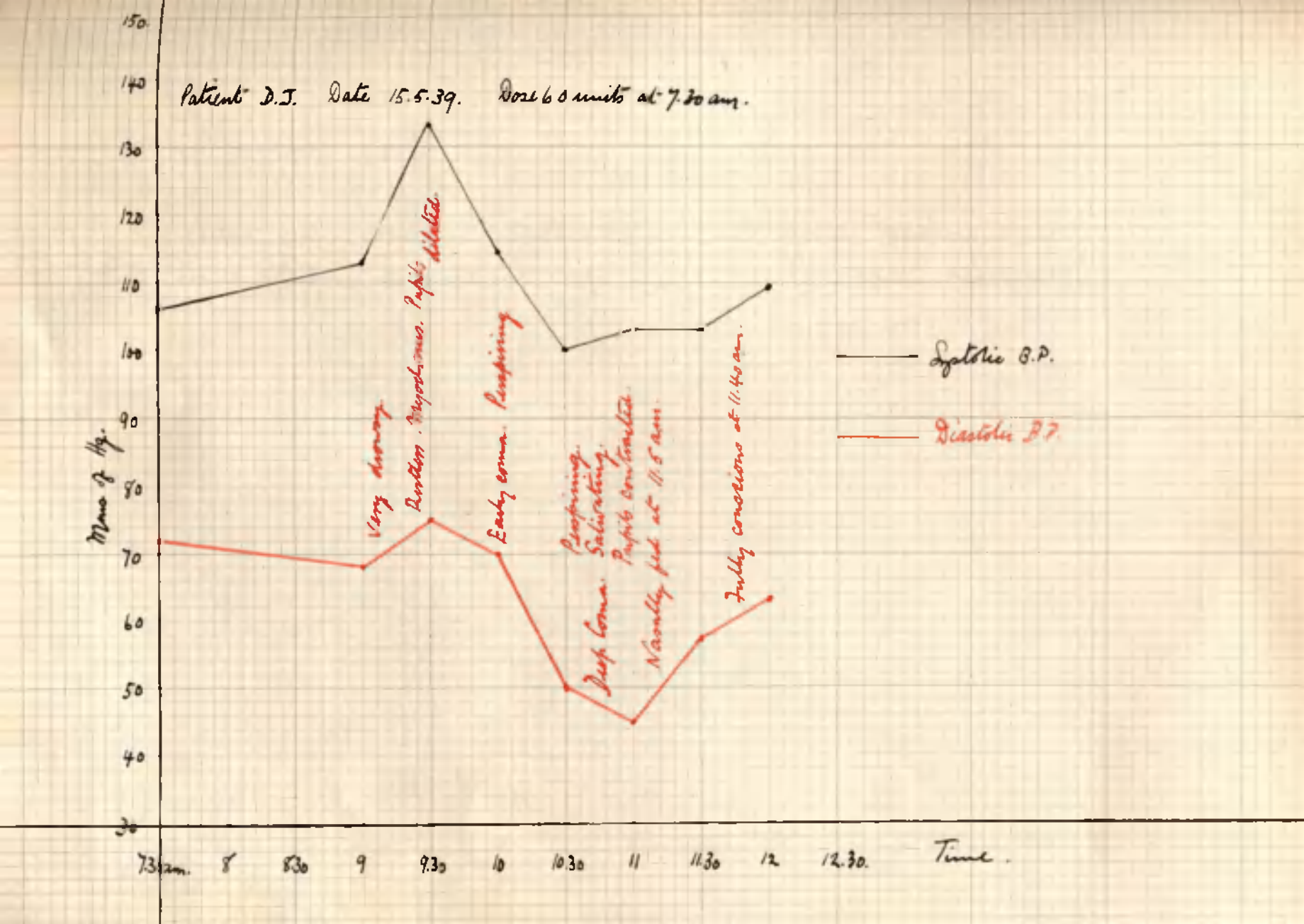
Entered at Stationers Hall Printed and Published by Waddington & C°s Gate Street Kingsway WC Gould's Clinical Chart


Patient D.J. Date 27.4.39. Dose 55 units at 7.30 am.
Some restlessness and Myoclonus.
Early coma.
Deep coma.
Normality felt.
Fully conscious.
Systolic B.P.
Diastolic B.P.
Mms. of Hg.
150
140
130
120
110
100
90
80
70
60
50
40
30
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30.
Time.

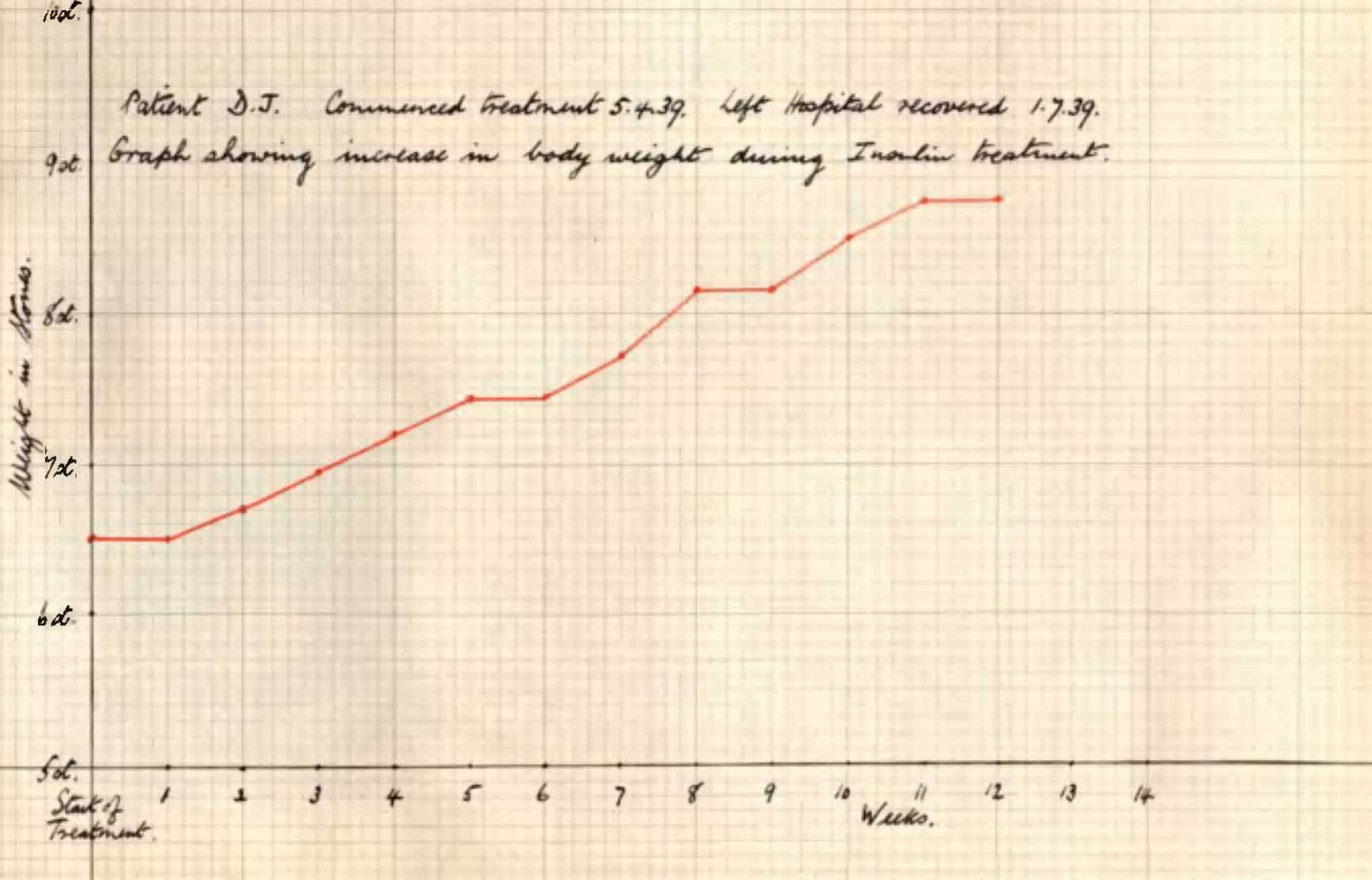

Patient D.J. Date 28.4.39. Dose 60 units at 7.30 am.
160
150
140
130
120
110
100
90
80
70
60
50
40
Mms. of Hg.
Drowsy.
Restless, Myoclonus. Pupils dilated.
Early coma. Perspiring.
Deep Coma. Perspiring. Salivating. Pupils contracted.
Fully conscious.
Systolic B.P.
Diastolic B.P.
7.30 am. 8 8.30 9 9.30 10 10.30 11 11.30 12 12.30 Time.


Patient D.J. Date 15.39. Dose 60 units at 7.30 am.
150
140
130
120
110
100
90
80
70
60
50
40
30
mm of Hg.
Redden. Myalgia.
Continued Restlessness. Pupils dilated.
Early coma.
Deep coma. Pupils contracted
Nearly fatal at 11.45 am.
Fairly conscious.
Systolic B.P.
Diastolic B.P.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.


Patient D.J. Date 13.5.39. Dose 60 units at 7.30 am.
150
140
130
120
110
100
90
80
70
60
50
40
30
Mms. of Hg.
Drowsy.
Restlessness.
Early coma. Perspiring.
Deep coma. Perspiring. Salivating. Pupils contracted.
Deep coma. Vascular tone at 11.32 am.
Fatally comatose
Systolic B.P.
Diastolic B.P.
7.30 am
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time


Patient D.J. Date 15.5.39. Dose 60 units at 7.30 am.
mms of Hg.
150
140
130
120
110
100
90
80
70
60
50
40
30
7.30 am.
8
8.30
9
9.30
10
10.30
11
11.30
12
12.30
Time.
Systolic B.P.
Diastolic B.P.
Very drowsy.
Restless. Hyperkinesis. Pupils dilated.
Early comm. Perspiring
Perspiring.
Salivating.
Pupils constricted.
Deep Comm.
Normality first at 11.5 am.
Fully conscious at 11.40 am.

Patient D.J. Commenced treatment 5.4.39. Left Hospital recovered 1.7.39.
Graph showing increase in body weight during Insulin treatment.



Another interesting case was that of M.H. whose photograph before and after treatment is shown. She was admitted as a voluntary patient on April 14th, 1939. Physically she was in fair health, her pulse was rapid, 100, her heart sounds were pure and she had somewhat prominent eyes. Mentally she was worried and anxious and when asked why she said that her whole life was being destroyed by a man's voice which she continually heard. The voice accused her of sexual offences. Previous to coming to hospital she had a good job as bookkeeper at a seaside hotel, there she had become friendly with a man and intimacy had occurred, she was then left by the man. She began to think that people were staring at her and talking about her and eventually she would not go out of the house. The hallucinations previously referred to then developed.

Before treatment.

After treatment.

This patient definitely appeared to be suffering from a degree of hyperthyroidism.

Treatment was started on a small dose of insulin, which was increased very gradually; at 60 units she had her first coma, this was of the wet type; during coma her pulse became very rapid. During her third coma, two days later, she developed a pulse rate of 160 and her pulse was irregular. The condition was identical with auricular fibrillation. Following the nasal feed she came round all right, the pulse slowed but was still irregular. Treatment was therefore suspended. During the time she was being built up to the coma dose there was a marked improvement in the patient's mental state, the hallucinations vanished; but following the suspension of treatment, the patient relapsed. As she had improved on small doses previously, it was decided to give her small doses of insulin short of the coma dose and for four weeks she had this treatment. On no occasion did she require to be fed nasally although she usually became drowsy and perspired. A marked improvement was noticed and the patient became much more settled in her outlook, the hallucinations vanished and she came to realise that the voices she had been hearing were only hallucinations. Her physical condition also improved, her pulse settled down to

a/

a normal rate and rhythm and her weight increased from 7 st. 10 lbs. to 8 st. 7 lbs. She eventually left hospital. In all this patient had only three comas.

Blood sugar tolerance tests were done on all patients and a list of the results was made in order to see if there were any abnormalities in Schizophrenics.

		Before Glucose	½ hr. after	1 hr. after	1½ hrs. after	2 hrs. after	2½ hrs. after	
(1)	B.C.	83	110	133	-	105	89	mgms per 100 ccs.
(2)	A.C.	83	149	175	-	130	111	"
(3)	M.R.	71	94	111	-	100	66	"
(4)	E.W.	80	104	122	-	94	85	"
(5)	L.C.	69	87	125	-	92	68	"
(6)	D.H.	74	87	108	-	93	71	"
(7)	E.F.	71	105	116	-	110	80	"
(8)	T.H.	66	-	122	-	66	-	"
(9)	E.C.	82	128	137	-	130	100	"
(10)	N.L.	126	162	166.5	160	156.5	125	"
(11)	D.D.	110	154	138	125	120	117	"
(12)	G.L.	106	120	142	158	135	126	"
(13)	E.Q.	88.5	106	121	130	105	-	"

		Before Glucose	½ hr. after	1 hr. after	1½ hrs. after.	2 hrs. after	2½ hrs. after.	
(14)	M.S.	85	99	107	122	115	100	Mgms.per 100 ccs.
(15)	D.J.	90	110	122.5	146	164	135	"
(16)	M.J.	105	165	215	195	155	110	"
(17)	D.L.	87	125	132	110	95	-	"
(18)	E.K.	62	71	84	75	65	-	"
(19)	M.D.	87.5	95	117	106	100	95	

In this series of blood sugar tolerance test curves it was seen that no characteristic curve occured in schizophrenia. Most of the curves lay within the normal limits, although one or two showed a definite lag in coming back to normal and a rather high and a rather low figure was seen here and there.

To date twenty cases have completed a full course of treatment. Twelve of these were discharged recovered and one went home partially recovered. The remaining seven are still in hospital. That is 65% of the cases treated so far are at home and at present all are doing well.

Below is given a table of the twenty cases who received a full course of treatment, showing the intervals between the first symptoms of illness and the commencement of treatment, and between the date of admission to hospital and the commencement of treatment.

Patient.	Time in months between first symptoms and start of treatment.	Time in months between admission to hospital and start of treatment.
A. Patients discharged.		
D.L.	4 mths.	4 mths.
L.C.	4 mths.	2 mths.
D.H.	28 mths.	15 mths.
E.K.	12 mths.	6 mths.
T.H.	4 mths.	4 mths.
E.C.	60 mths.	-
M.D.	2 mths.	2 mths.
E.Q.	2 mths.	2 mths.
M.S.	14 mths.	-
D.J.	2 mths.	1 mth.
D.D.	12 mths.	½ mth.
M.J.	10 mths.	10 mths.
M.H.	4 mths.	-
Total	158 mths.	
Average	12.1 mths.	Average 3.5 mths.

Patient.	Time in months between first symptoms and start of treatment.	Time in months between admission to hospital and start of treatment.

B. Patients not discharged.

B.C.	96 mths.	7 mths.
A.C.	10 mths.	8 mths.
M.R.	12 mths.	8 mths.
E.W.	24 mths.	3 mths.
E.F.	16 mths.	7 mths.
N.L.	33 mths.	27 mths.
G.L.	16 mths.	14 mths.
Total	207 mths.	
Average	29.5 mths.	Average 10.5 mths.

It will be seen from the above table that, as reported elsewhere, treatment early in the disease is much more effective than late.

V. DISCUSSION.

The autonomic nerve supply to the pupils is the Sympathetic to the dilator pupillae and the Parasympathetic via the third cranial nerve to the sphincter pupillae.
In my series of cases the outstanding feature was the constriction of the pupils when the patient was in deep coma; there was a gradual diminution in size all morning; this was seen especially well in those cases who passed into coma very quietly without a restless period; in all cases though an interesting point was noticed that the pupils could be made to dilate if the patient was interfered with or stimulated, this dilatation came on after a short latent period of 1-2 secs., remained for 10-20 secs. and then passed off.
From these two points it appeared that as hypoglycaemia developed there was a tendency towards parasympathetic predominance but at the same time the sympathetic system was ever on the alert and ready to act. In several patients, entry into coma was not quiet and peaceful, various degrees of restlessness and myoclonus were encountered. During every bout of restlessness and myoclonus there was a dilatation of the pupils and also an increase in the pulse rate, it appeared as if at these times there was a sympathetic predominance. The reasons for this assumption were :-

(1) Cannon and Britton[63] stated that hypoglycaemia stimulated the liberation of adrenaline into the blood stream.

(2) The latent period of 1-2 secs. between the stimulus and the pupil dilatation corresponded with the time it would take adrenaline to reach the pupil from the supra-renal glands. This latent period was so long as to exclude a purely nervous reflex mechanism (i.e. either direct sympathetic stimulation or parasympathetic inhibition).

(3) The dilatation continued steadily and progressively for some seconds after the cessation of the stimulus and then steadily declined. (This also excluded a purely nervous reflex).

(4) Successive slight stimuli, such as repeated taps at intervals of three seconds caused successive waves of dilatation with a latent period after each stimulus.

(5) The dilatation was accompanied by a rise in pulse rate.

These observations indicated that there was not a predominance of one or other of the two sides of the autonomic system throughout the hypoglycaemic period but rather that there was an oscillation between these two states. When there was a prevalent tone of either system, this seemed

to/

to be due to increased activity of that system rather than inhibition of the other. Thus during a typical coma there was first a period of parasympathetic tone (gradual constriction of the pupils) then a period of predominant sympathetic tone (restlessness, pupils dilated) followed by a stage of coma in which there was a parasympathetic tone. Throughout this period the pupils dilated rapidly on slight stimulation of the patient and this appeared to be due to the release of adrenaline which converted the previous parasympathetic tone into one of sympathetic tone. This indicated that even when there appeared to be parasympathetic prevalence, the sympathetico - adrenal apparatus was reflexly hyper-excitable. Conversely during the restless myoclonic stage, when the pupils were dilated and there appeared to be a state of sympathetic prevalence, there was a constant tendency for the pupil to return to a contracted state, if between the waves of restlessness there was a period of quiet calm. The parasympathetic system must also have been hyper-excitable.

These findings differed from those of Wespi[64] who stated that neither a parasympatheticotonic nor a sympatheticotonic state of the organism could be provoked by insulin treatment. On the contrary, in one and the same individual, and under apparently identical conditions, the

pupils/

pupils may show one day sympathetic dilatation and the next day parasympethetic constriction.

Regarding the behaviour of the blood sugar in schizophrenics, many workers have written. Wuth[65] found no definite abnormalities, although high values in anxious cases. Newcomen[66] and Weston[67] obtained normal values. Mumford and Parkin[68] found high values in some cases, which they attributed to a high degree of psychomotor activity. Uyematru and Soda[69] found a raised blood sugar in 47% of thirty two catatonic cases two and a half hours after a meal. Roggenbau[70] found variations from the normal, but described no characteristic changes, although actually a few high figures were to be seen in his results.
Reiter[71] found hyperglycaemia in some cases and renal glycosuria in others.

The sugar tolerance test of Janney and Isaacson[72] or blood sugar curve has attracted many workers. Kooy[73] found some abnormally high curves but believed that these only occurred in depressed or anxious cases. Bowman, Eidson and Burladge[74] found abnormally sustained curves appearing in their cases in an inconstant manner. Raphael and Parsons[75] found in an investigation of eleven cases the

fasting/

fasting level below the normal, the acme higher and the return to the initial level unduly delayed, namely for longer than two hours. Lorenz[76] found high sustained curves in catatonic cases, but very low flat curves in simple deteriorating cases. Schwab[77] found an initial rise far beyond the normal and a delayed return to normal in some cases. Henry and Mangan[78] also found high sustained curves, which they attributed to retardation of the functions of the autonomic system. Schryver[79] found low fasting values and high sustained curves in some cases. Barret and Serre[80] found in thirty cases marked variations in the same individual at different times. Drury and Farran Ridge[81] in an investigation of eighteen cases found very high and rather broad curves in acute cases, higher in female subjects than in males, and small low curves in chronic cases, lower in males than in females. Mann[82] found unduly sustained curves in cases of stupor; Kasanin[83] examined forty cases and collected a further one hundred and fifty four from the literature, believing as a result that no characteristic curve occurred in dementia praecox, but that individual curves varied greatly from the normal, being sometimes too high, sometimes too low and sometimes too sustained. Pfister[84] found in normal persons a brief but steep rise

after/

after the glucose was given, then a gradual fall. In schizophrenic patients the result was different. The acute cases showed a rapid rise exceeding by many times the normal value and a relatively slow fall. The ergotropically excited schizophrenic organism retained in the blood ready for use great quantities of sugar over a long period. With chronic schizophrenia on the other hand, the blood sugar rose very slowly, often failing to reach its maximum in two hours. This was evidently the result of the delayed absorption of sugar and another expression of a weakness in the autonomic system.

Many of these opinions were varied and it appeared to me that there was no characteristic change in the blood sugar curve of schizophrenics and my own series of cases shown before confirmed this.

When insulin was injected into a normal subject it acted in essentially the same way as it did when administered to a diabetic patient; but by disturbing the existing well regulated state of metabolism it would produce toxic manifestations. The body would react to these disturbances in various ways and would attempt to restore the normal condition of affairs. The effects produced by insulin would

therefore/

therefore be complex and would consist partly of the direct actions of the hormone and partly of the compensatory reactions of the body.

Samson Wright[85] stated that following the subcutaneous injection of insulin there was a fall in the blood sugar level which reached its lowest level after half an hour to several hours according to the dose employed. In rabbits, at a blood sugar level of 45 mgms. per 100 ccs there was a loss of muscle tone, violent convulsions at intervals, subnormal temperature and finally death. The convulsions were due to the fall of blood sugar stimulating centres in the pons and medulla; convulsions still occurred in the decerebrate animal, but not after the medulla was destroyed. If the dose of insulin was not too large the blood sugar returned to normal owing to the compensatory mobilisation of the liver glycogen. Hypoglycaemia was therefore most pronounced and prolonged when the liver glycogen stores were low and recovery of the blood sugar level did not occur after hepatectomy. The response of the liver was due to the low level of the blood sugar acting on the central nervous system; impulses passed via the sympathetic nerves directly to the liver and there was also a liberation of adrenaline.

When insulin was given there was firstly an increased utilization/

utilization of sugar by the tissues and an increased storage of glycogen by the muscles and probably also by the liver - this rapid removal of sugar from the blood was not however a complete explanation of the hypoglycaemia. Samson Wright[85] stated that there was also an arrest of the sugar formation from protein in the liver because if a starving animal with a glycogen depleted liver took a great deal of exercise, sugar was undoubtedly removed from the blood to the tissues but yet the blood sugar level did not drop; as the sugar did not come from glycogen in the liver it must have been produced in the liver from protein. Therefore insulin produced an hypoglycaemia by causing the tissues to remove sugar from the blood and by preventing the liver from producing fresh sugar from protein.

At a certain level in the fall of blood sugar, a compensatory mechanism began to work, adrenaline was secreted and reinforced the nervous messages passing to the liver from the central nervous system, this mobilized the liver glycogen and tended to arrest the fall in blood sugar. Samson Wright[85] found that if the sympathetic nerves to the liver and suprarenals were paralysed with ergotoxin the compensatory mechanism did not come into action and the recovery of the blood sugar either did not occur or was very slow. If a

convulsion/

convulsion took place, there was a fall in the glycogen level of the muscles and this appeared to me to be a further compensatory mechanism.

In the series of blood sugar estimations which I did I found that the greatest fall in the blood sugar took place in the first one and a half to two hours; during this time the only symptom was drowsiness; following this there was a tendency towards a straightening out of the line of the graph; in some cases the blood sugar level fell further but not so steeply, in others it fell a little further and then rose, in others it continued at almost the same level and in others it rose. During this period coma commenced and it appeared to me that coma did not depend on the blood sugar level alone but also on the duration of the hypoglycaemia. In certain cases, usually following a bout of restlessness, the blood sugar level rose somewhat, this appeared to be due to the restlessness which was of a compensatory nature, the muscles liberating lactic acid to form glycogen in the liver. The ordinary compensatory mechanism must also be remembered. The most usual coma values were 20-35 *mgms.* per 100 ccs. and these corresponded with those of Reese and Veer[38] and Freudenberg[50].

Freudenberg[50] also found that the first symptoms of hypoglycaemia made their appearance the earlier, the more rapid and the greater the fall in actual blood sugar values was. For the most part they came on after the initial fall. Coma began only when the blood sugar had been below 30 mgms. per 100 ccs. for at least one hour and twenty minutes.

In the first rapid fall of the blood sugar, the tissue cells probably absorbed sugar more quickly than they used it, as a result of this, by the time actual deficiency made itself felt in the cells, the blood sugar had sunk very low without any serious symptoms being manifested. Then the deficiency stimulated the compensatory liberation of sugar from the liver and muscles, and although this might lead to some rise in the blood sugar the "head" of sugar in the blood was now insufficient to supply the cells, whereas previously an even lower blood sugar occurred without symptoms being apparent, because of the initial store of sugar in the cells.

Georgi[86] explained the rise in blood sugar occurring during coma as being due to a transference of sugar from the body cells to the blood and upon the withdrawal of the sugar from the cells of the central nervous system that clinical phase began in which we observed the well known so-called

hypoglycaemic/

hypoglycaemic symptoms. This appeared strange to me, for why should the body allow sugar to be withdrawn from the cells when they were urgently in need of it. A more possible explanation appeared to be the simple compensatory mechanism coming into action, namely that when the cell sugar touched a certain low level, the Sympathetico-adrenal apparatus came into action and mobilized sugar from the liver glycogen. In the great majority of cases, the mechanism was not strong enough to bring the patient round but occasionally if associated with a period of restlessness (also a compensatory mechanism) the patient came round completely. It was also noticed that when a patient had been very restless, she came round quicker after a nasal feed, than another patient who had been the same time in a state of quiet coma. It seemed to me that this compensatory mechanism might vary in different patients thus fitting in with the possibility that schizophrenia was a disease of the autonomic regulating system.

With regard to the pulse records, in my cases, in the early quiet phase, there was some tachycardia and this was especially marked if the quiet phase was followed by a restless myoclonic phase; as coma developed the pulse rate definitely slowed but if the patient was disturbed it temporarily speeded up. It appeared to me that during the restless phase there

was/

was a sympathetic prevalence followed as coma developed by a parasympathetic prevalence. Other writers' views were :- Russell[87] stated that the pulse rate usually rose as shock continued, bradycardia being rarely seen. Wilson[47] stated that in the early stages of hypoglycaemia the pulse was often increased in rate, later on bradycardia set in and sometimes after a transitory period of irregularity it slowed down to 40. Accornero[88] stated that under the action of high doses of insulin, the pulse generally accelerated during the first hour of shock. Towards the end of coma the pulse became slow. Appreciable variations were noticed from one minute to another.

The blood pressure rose in the early part of hypoglycaemia corresponding to the increase in the pulse rate and also to the restless myoclonic phase; this appeared to indicate a sympathetic prevalence. As coma developed the blood pressure fell corresponding to the slowing in the pulse rate; this appeared to indicate a parasympathetic prevalence.

Lovat Evans,[89] Wiggers[90] and Samson Wright[85] stated that there was still a lack of uniformity of opinion as to the accuracy of diastolic readings and even the point which it was best/

best to take as indicative of this pressure. In my series of readings, the fourth phase of the diastolic sounds i.e. when they begin to fade for the second time was taken as the diastolic pressure.

Hadorn[39] stated that during hypoglycaemia the blood pressure rose; as a rule the systolic pressure showed a slight rise (10-20 mms of Mercury) and the diastolic a slight fall. Stokvis[91] found that the blood pressure sunk below normal and showed more variation than was normal. G.A.Young, R.H.Young and Roulk[92] found that there was an almost uniform rise in the systolic pressure and some fall in the diastolic pressure to produce an increased pulse pressure during the shock period. On taking the blood pressure during the evening or on the rest days after the treatment had been in progress for some weeks a lowered blood pressure was found and occasionally a systolic pressure between 85 and 100. Accornero[88] stated that with moderate doses of insulin, the blood pressure was raised; with high doses, however, the pressure presented an ascending curve which reached its maximum at the moment of the most marked hypertonia, then when the false hypertonia set in the pressure tended to diminish but it rarely became lower than the patient's normal. Georgi[86] found that parallel with the fall in blood sugar to,

or/

or almost to, its lowest level was the increase in pulse rate, which, aside from its acceleration caused by the state of excitation rose to the maximum in the second hour and subsequently again decreased. The same held good for the blood pressure, the amplitude of which reached its first peak between the second and third hours.

From these observations on the pupils, blood sugar, pulse rates and blood pressure, it appeared to me that following the injection of insulin there was a stimulation of both sides of the autonomic nervous system, at one time the stimulation being more marked in the parasympathetic system and at another time more marked in the sympathetic system.

Early drowsy phase.	pupils becoming smaller	- Parasympathetic prevalence.
	pulse rate increasing blood pressure rising	- Sympathetic prevalence.
Restless phase.	pupils dilated pulse rate quickened blood pressure raised	- Sympathetic prevalence.
	During a lull in the restlessness the pupils became smaller	- Parasympathetic prevalence

	(pupils contracted)	
	(slow pulse)	
	(blood pressure falling)	- Parasympathetic
	(increased perspiration)	prevalence.
	(increased salivation)	
Deep coma.	(	
	(	
	(If the patient was)	
	(disturbed the pupils)	- Sympathetic
	(temporarily dilated)	prevalence.
	(and the pulse temporarily)	
	(speeded up.)	

Some experiments are now being tried with the object of changing the patient's natural reaction to insulin i.e. if she reacts with a quiet wet type of coma, an attempt is made to change her reaction to the so-called dry type of coma in which fits are more common and vice-versa. Atropine is being tried in the attempt to change the wet type of reaction to the dry type and acetylcholine to change the dry type to the wet type. Up to date the results are promising, but it has not been tried often enough. More work is necessary in this direction.

I asked my nursing staff what they thought of the treatment, were the patients easier to manage ? Their answer was a unanimous yes; even if the psychosis was not removed, the patient was much easier to handle. I never found it necessary to give a sedative during the whole of treatment.

Having personally supervised over a 1000 hypoglycaemic comas, I am convinced that the new treatments are a step in the right direction but many more cases will have to be treated and those cases who have been discharged must be followed up carefully at regular intervals.

Every case should be treated :

(1) By her natural reaction to hypoglycaemia for at least six weeks.

(2) If she does not improve, an effort should be made to change her type of hypoglycaemic reaction.

(3) If no improvement occurs, interruption in different periods of the hypoglycaemia should be tried e.g. instead of interrupting in the coma stage, interrupt in the restless stage.

(4) If there is still no improvement, cardiazol should be given.

(5) If the patient improves with cardiazol, a further course of insulin probably aids the permanency of the cure.

(6) It is essential that treatment should be continued as long as there is the slightest evidence of improvement.

Fifty insulin comas is the absolute minimum that should be given before giving up.

VI. S U M M A R Y.

(1) An account of schizophrenia and its various types is given.

(2) The technique of the insulin and cardiazol treatment is given in detail along with complications and theories regarding the rationale.

(3) Five cases treated with insulin are described in detail and the results of experiments on the pupils, blood sugar, pulse rate and blood pressure are shown. A table of results is given.

(4) The rationale of the treatment is discussed and a stimulation of both sides of the autonomic nervous system is shown to occur.

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