

ACUTE YELLOW ATROPHY OF THE LIVER, WITH SPECIAL REFER-
ENCE TO ITS ETIOLOGY, TREATMENT, AND ASSOCIATION WITH
PREGNANCY, WITH A REPORT OF TWO CASES OCCURRING IN THE
PUERPERIUM.

by

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THESIS PRESENTED
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INTRODUCTION.

The growth of all human knowledge depends primarily on the accumulation of evidence and the collection of accurate observations, followed by careful sifting of that evidence with precise and unbiased consideration of all the facts so garnered. Thus it comes that in our search for the fundamental causes of human ills, no detail however trivial should be overlooked, and no information be withheld. Further, by the correlation and comparison of such evidence from widely varying sources, previously unrealised factors may become apparent; the trivial detail of no apparent importance may assume the highest significance in the light of others experience. Our forbears in medicine fortunately appreciated this, and I quote Barlow who wrote thus in his introduction to the first of Guy's Hospital Reports in 1836. (1) "Without personal observation, medical science must decline; without recorded experience, it must at best be stationary, and it is only by a union of the two, that it can be rendered cumulative and traditive, and consequently progressive".

So, in choosing for my subject Acute Yellow Atrophy of the Liver, I have been guided first by its extreme rarity and our lack of knowledge of its etiology and treatment, secondly by the unusual chance that/

that I have myself encountered two such cases in general practice, both of which occurred in the puerperium. Thirdly by the fact that one of the cases recovered completely, and recovery being only too seldom the outcome of this very fatal disease I feel it should be recorded. Moreover in recording it I am including all the details at my disposal, many of which may seem trivial and irrelevant, but which may assume greater significance in the light of increasing knowledge.

OUTLINE OF THESIS.

I propose therefore to begin by reporting as fully as possible my two cases of Acute Yellow Atrophy of the Liver; and to follow this by a detailed consideration of them in the light of the accumulated literature on the subject, paying especial attention to the clinical, etiological and therapeutic aspects of the disease and its association with pregnancy, and surveying where possible the state of our knowledge of the disease and its pathology. In studying the disease I have been hampered somewhat by a lack of knowledge of German, in which language some of the important literature has been written, so that some of my references are unverified since I have had to rely on other workers interpretation/

interpretation. Finally I hope to summarise the conclusions I have arrived at.

ACKNOWLEDGMENTS.

I acknowledge with gratitude the help I have received from Professor Johnstone in permitting me to consult and use the case records of the Simpson Memorial Hospital; from Dr. Robertson, the Registrar of the "Simpson", in tracing these records; from Dr. Miller of the Pathological Department in placing microscopic sections at my disposal; and from the Librarians of the Central Medical Library in their constant assistance in connection with the literature.

CASE RECORDS.CASE 1. Mrs. A.

The patient was a normally healthy woman of average size and weight, of good nutrition, aged 32 years, the wife of a doctor and mother of one son born eleven years previously. She herself was a premature baby (eight months) and was severely ill with summer diarrhoea when three months old, and suffered from bronchitis every winter until the age of five. Other illnesses were severe scarlet fever, severe measles, whooping cough and chicken pox in the first decade of life, and mumps at the age of twenty. There was no history of any of her illnesses being complicated by nephritis. Menstrual history was normal, 4-7/28 in type, regular and uneventful.

She first became pregnant at the age of 21 in 1925; she was not then under my care but I have obtained notes on her history from her doctor of that time. A general oedema and progressively increasing albuminuria appeared about a month before term and persisted in spite of rest in bed and a restricted low protein diet. Labour was induced by the insertion of bougies a fortnight before term, and proceeded normally. Chloroform was administered for both induction and delivery. The puerperium was uneventful, all symptoms of toxæmia disappearing quickly.

Following/

Following the confinement the patient made a good recovery and enjoyed good health, with the exception of two attacks of fibrositis affecting the muscles of the left shoulder girdle, and occasional winter colds, two of the latter being accompanied by mild pyrexia of two or three days duration.

In the summer of 1935 tonsillectomy was advised, as the tonsils were grossly unhealthy and were suspected as the etiological factor in the occurrence of the fibrositis, but more especially with the purpose of improving the general condition of the patient with the view to a second pregnancy. The tonsils were dissected in June 1935 under chloroform anaesthesia, induced by the open method and maintained by a Junkers inhaler. The operation and convalescence were uneventful apart from severe and intractable post-anaesthetic vomiting for thirty-six hours following the operation. A radiographic examination of the chest at this time revealed no evidence of abnormality in the lungs. In the year following the operation the patient enjoyed very good health. Repeated physical examination and observation throughout the year was entirely satisfactory, the urine and blood pressure were always normal, a water elimination test carried out by the STRAUS-GRAUNWALD method (2) gave a satisfactory/

satisfactory result, and no evidence of a septic focus was detected. During this year the patient had a month's cruising holiday and herself stated that she felt very well indeed.

In 1936 the patient again became pregnant, the last menstrual period commencing on May 21st, the expected date of confinement being therefore calculated to be Feb. 28th 1937.

The first trimester was uneventful. Morning sickness occurred two or three times during the third month, and nausea was frequent but was relieved by the taking of carboserin (Bayer medicinal charcoal) one tablet after each meal, and later by betanaphthol, charcoal and peppermint tablets (Oppenheimer). Otherwise the patient was very well and that these symptoms were not severe is evidenced by the fact that the patient was in active charge of a Girl Guide camp for a fortnight during August. Throughout the patient was kept under close observation, including frequent blood pressure estimations and urine tests. It was noticed during the second trimester that the patient had an unusually good appetite, and towards the end of this period there was a marked general increase in size and weight. At the end of October the patient had an acute coryza, this was unaccompanied by pyrexia or any obvious general disturbance; the acute stage passed in the normal time but left a mild chronic nasopharyngeal catarrh/

catarrh which occasionally flared up into a brief coryza and still persists in spite of varying forms of treatment. About this time too occasional cramps in the limbs were complained of, especially at night, the B.P. was 128/84. The patient was put on calcium lactate D Gr. $7\frac{1}{2}$ three times a day with Adexolin capsules two daily. No further trouble was experienced with cramp throughout the pregnancy.

In November the pulse rate became accelerated from the patient's normal rate of 76-78 up to 90. This persisted, no other abnormality was detected, the B.P. was 120/80, the patient did not complain. Extra rest was advised. On December 6th the B.P. was found to be 130/90, urine normal, and a tendency to dilatation of the small veins of the face was observed. Meat was reduced in the diet to once a day. By December 20th the B.P. was 140/90 and about this time on two separate occasions the patient's nights were disturbed, once by a severe headache, once by an attack of vomiting. Meat was cut out of the diet completely and protein restricted to fish or egg once only in the day. Daily urine examinations were instituted and more frequent blood pressure estimations made. Towards the end of December there was apparent clinically, a puffiness of the face, hands and feet, though no pitting on pressure was present. The patient herself made no complaints.

On/

On January 16th albumen appeared in the urine, the amount being less than 0.5 grams per litre. The systolic blood pressure rose to 158 and there was slight pitting of the hands and feet on pressure. The patient was confined to bed on strict diet (vide infra). The dose of adexolin capsules which had been continuously taken was increased from two to three capsules a day. The calcium which apart from two short periods, had also been taken continuously was changed from calcium lactate D to calcium gluconate (Borroughs Welcome) five tablets of gr. 20 each, during the day. The bowels were kept well open without difficulty by the use of liquid paraffin and infusion of senna pods, eight to ten pods on alternate days being all that was required to obtain a very satisfactory motion. From this time onwards daily B.P. estimations were made and charted along with the amount of albumen present, estimated by Esbach's Picric Acid Albuminometer, and the amount of urine passed in the twenty-four hours. Regular ophthalmoscopic examinations were made, no abnormality was ever detected in the retina, though this may have been due to inexperience on the part of the examiner. An attempt was made to regulate the intake of fluids in accordance with the amount of urine passed but as this resulted in a progressive diminution in the quantity of urine it was abandoned and abundant fluid allowed, though not pushed.

Throughout/

Throughout the following ten days the condition of the patient varied little from day to day. Symptoms complained of were heartburn, intermittent slight headache and mild temporary depression, but otherwise the patient affirmed that she felt quite well and comfortable and she usually appeared quite cheerful and happy. The heartburn was moderately severe, and occurred frequently but was relieved by a simple kaolin mixture. Objectively marked pallor was observed from time to time, both by myself, the nurse and the patient's husband.

Oedema of the hands and feet with pitting was usually present though never marked, and moderately free perspiration occurred during some nights. The amount of albumen in the urine varied little, except on one occasion (January 20th) when it rose to 1.0 gram per litre, to return to 0.3 grams per litre the following day. The systolic blood pressure was usually in the region of 155 with a range of 140 to 165. One evening temperature of 99.2 was recorded on January 22nd. A urine urea estimation on this date gave 1.18%. ~~xxxxxx~~
~~xxxxxxxxxxxxxxxx~~ A blood urea estimation taken on January 24th gave a reading of 26.0 milligrams per cent. On January 25th five tablets of calcium lactate D per day (a dose of $37\frac{1}{2}$ grains daily) were substituted for the calcium gluconate, as the latter were not tolerated by the patient, producing nausea.

Following/

Following this on January 26th there was an abrupt rise in the amount of albumen in the urine, and the patient was removed to a nursing home by ambulance, a distance of some sixty miles, on January 27th. Throughout this time there had been no evidence of ill-effect on the foetus, heart sounds were uniformly well heard and the rate was within normal limits, movements were normal, the size of the uterus was in agreement with the length of pregnancy and was increasing normally. Painless contractions of the uterus were frequently observed, both by myself and the nurse. The findings on the day of removal to the nursing home were systolic blood pressure 150, albumen 4 grams per litre, amount of urine only 12 plus ounces. The pulse was 76 and temperature 97.8. Induction of labour was proposed unless marked improvement was exhibited during the next twenty-four hours. It was felt desirable that the patient should have a night's rest after her journey, prior to being subjected to any interference. The following day, January 28th, the B.P. was 155, albumen two grams per litre, and the amount of urine only 6 plus ounces. An enema was given with a good result, and gr. 1/100th of atropine prior to anaesthetisation. In view of the possible necessity of giving chloroform later, ether alone was used for the operation. Two gum elastic bougies were inserted between/

between the uterus and the membranes, without rupturing the membranes, the ends of the bougies just protruding from the cervix were maintained in position by a short piece of gauze loosely wrapped around the cervix and bougies. No attempt was made to pack the vault of the vagina.

This procedure was carried out at midday and during the succeeding afternoon and evening the patient was continually retching and had a moderate amount of vomiting. When seen in the evening the general condition was quite good though the pulse was 116 but of good volume and regular, the tongue was moist and clean, the bowels had moved and 4 ounces of urine had been passed. Throughout this day the patient had had no food and very little fluid, first in preparation for the anaesthetic, and later on account of the vomiting, most of the fluid taken by mouth being returned. A restless night followed with the vomiting persisting, but this ceased by morning and the patient said she felt better although she complained of general stiffness. The presentation was vertex.

Labour pains commenced at 9.15 a.m. and continued throughout the day. They were regular but not sufficient to distress the patient. At 5 p.m. there was a show and pains increased in strength during the evening. Chloroform administration was commenced at approximately/

approximately 9 p.m. being administered by means of a Junker's Inhaler attached to an open mask, by the patient herself, only during pains which were then occurring every six or seven minutes and were strong. At 10.15 p.m. the patient was delivered naturally of a live 6 lb. 3 oz. female child, the control of the anaesthetic being taken over by the nurse and given continuously (still by Junker) for approximately ten minutes at the actual time of delivery. The loss was normal. The cord was abnormally thick, with the skin of the abdomen extending $1\frac{1}{2}$ to 2 inches along the cord. At 11.10 p.m. the placenta not having delivered itself, was expressed manually by Credes method without difficulty, it appeared quite healthy but larger than normal; no record of its weight was made. Pituitrin 1 cc. was injected following the birth of the placenta. The temperature after delivery was 99.6, pulse 116, of good volume and diminishing in rate. The total duration of labour was thus fourteen hours, and no pelvic examination had been found necessary. The total duration of chloroform administration, both continuous and intermittent was approximately one hour and a quarter, and the total amount used about one ounce. Unfortunately the exact amount is not known as some was spilt in measuring it, but including the amount lost only one and a half ounces was used.

THE PUERPERIUM.

FIRST DAY (January 30th). Following the delivery the patient slept very poorly, complained of nausea and tried to vomit. There was marked pallor during the night and a pulse rate of 118 but no other evidence of bleeding, this was explained by the passing of a large clot towards early morning. The condition was improved in the morning, pulse 96, but the patient still complained of nausea and retching though very little vomit was brought up. This was relieved somewhat by 50 cc. of intravenous dextrose (20%), after which the patient slept for a while and took fluids, sips of champagne and a few plain biscuits on waking. The bowels moved and 32 ozs of urine was passed in the twenty-four hours, in which albumen was still present in fair amount. B.P. was 155. Nembutal gr. $1\frac{1}{2}$ was given at 10 p.m.

SECOND DAY (January 31st.) Slept for two hours after the nembutal of the previous evening, but was very wakeful after that and at 8 a.m. became very restless, later complained of nausea and began to vomit small amounts of mucus mixed with blood. When seen at 10 a.m. she complained of very great weakness, was inclined to apathy but very restless and frequently retched and vomited small amounts. The vomit gradually changed from bloody mucus to coffee ground vomit, later still it became entirely black. There was slight jaundice/

jaundice, which increased rapidly in amount during the day. Temperature was 97.6, pulse 120, of poor volume, the tongue was moist and coated. B.P. was 150. Reflexes were very brisk, plantar reflex was flexor in response. The uterus appeared to be involuting normally, and the lochia was normal. Urine had been passed and contained bile and albumen, no sugar. The liver dullness was diminished (the lower border being two fingers breadths above the costal margin), but there was no tenderness in the liver or any other area of the abdomen. A diagnosis of Acute Yellow Atrophy of the Liver was made, and confirmed both by my partner and by a consultant gynaecologist (Mr. Leslie Dodds) later in the day. The intravenous 20% dextrose was repeated.

The patient continued to be very ill all day, and fluids were not well retained when given by the mouth. Calomel gr. $\frac{1}{4}$ every hour to 2 grains was given, and followed by magnesium sulphate half an ounce. A pint of 10% glucose was given intravenously at 9 p.m. and followed by 10 units of insulin. This was repeated without the insulin at 3 a.m. Throughout the night the patient was gravely ill, retching frequently with little result, pale, drowsy and apparently very weak. The pulse was feeble and irregular, being uncountable at/

at times, but improving after the second intravenous infusion and towards morning there was general improvement, the retching ceased and 1 drachm of sodium bicarbonate given orally was retained. The bowels moved well, the stool being pale but not clay coloured.

THIRD DAY (Feb. 1st.) There was improvement which continued all day, the patient was able to retain fluids and took freely of ice, orange juice and water, and milk and soda, both with glucose. Apathy disappeared, jaundice was less though liver dullness remained diminished. In the evening the pulse rate fell to 96, the bowels moved well twice during the day, the stool being pale. The amount of urine passed was increased, whilst the amount of albumen it contained was still decreasing and continued to fall from then onwards, bile was still present and markedly so. Paraldehyde was given per rectum, and though it was not well retained the patient had a fair night.

FOURTH DAY (Feb. 2nd.) The improvement of the previous day was not maintained, and though the patient was able to take fluids freely drowsiness was present, becoming rapidly worse throughout the day and the jaundice was more prominent. Urine however was passed freely. The patient was visited by a consultant physician (Dr. Douthwaite) who agreed with the clinical findings and confirmed/

confirmed the diagnosis. At his suggestion 2 cc. of anhaemin was given intramuscularly. The calomel and magnesium sulphate was repeated and oral fluids were pushed, the patient being roused to drink every half hour. The fluids given were, fruit juice and glucose water, milk and soda with marmite and glucose, and ice. At one period fifty ounces of fluid was given in five hours.

FIFTH DAY (Feb. 3rd.). Fluids were continued at half hourly intervals throughout the night and the succeeding day. The condition was much the same, the patient being semi-conscious throughout, though fortunately capable of swallowing which she did whenever her mouth was filled. A curious feature was that although no response could be elicited by shouting to or even shaking the patient, yet she chewed up pieces of ice placed in her mouth with a loud crunching noise that somewhat eerily broke the stillness and quiet of the ward. During this day the pulse varied from 116 to 146 and was of poor volume, and towards evening twitching of the facial muscles was observed and respiration tended to be stertorous; the pupils were widely dilated. The tongue was very coated and the lochia was slightly offensive. The temperature was 99.6. The B.P was lower on this day.

SIXTH/

SIXTH DAY.(Feb. 4th) A small piece of membrane was passed and thereafter the lochia was normal. The patient was still very drowsy and not able to be roused, but towards evening it became more difficult to make her drink and she seemed to resent interference. The mouth and throat were very coated and the tongue dry. Jaundice was still marked.

SEVENTH DAY. (Feb. 5th) The pulse was improving, slower and fuller, and the normal liver dullness was restored. The patient roused once and spoke for the first time for three days. Improvement in clinical signs followed throughout the day and in the evening the patient again roused for a few minutes and spoke quite normally asking what had happened. Jaundice was still marked, and the urine though plentiful still contained a gross amount of bile. Albumen was reduced to below 0.1 grams per litre and the blood pressure was approaching a normal level. The oedema had by now completely disappeared.

EIGHTH DAY. (Feb. 6th) The improvement was maintained and the patient was able to take groats and milk jelly. The stool was clay coloured on this day and jaundice was still marked. From this point the physical condition improved rapidly, the patient only complaining of "limpness" and weakness. Mentally she was very confused/

confused for some twenty-four hours after regaining full consciousness, but this was transient and within a fortnight she was able to get up and sit in a chair for half an hour.

She was fit for discharge from the nursing home four weeks after admission but was confined to her bedroom at home for some little time. She was kept on a low fat and protein diet for several weeks, the protein being gradually added first, then with a little fat, the fat being the last food to be fully restored to the diet.

Convalescence was protracted and interrupted a month after her return home by the occurrence of generalised muscular aching, associated with a few days mild pyrexia and excessive weakness. There was some perspiration at night during this period, but examination revealed nothing to account for the pyrexia. These symptoms disappeared after ten days rest in bed and the exhibition of aspirin in small doses. It was thought at the time that the patient had been overdoing things. Recovery then proceeded uninterrupted and when last examined three months ago the patient was leading a normally active life, the urine being free of albumen and the blood pressure normal. During the convalescence, iron and incretone were given as tonics, and the menses recommenced after four months and have been regular ever since. The only sequelae that the patient has/

has noticed is that on a few occasions, usually following the taking of rich food, she has had an attack of sickness lasting two or three hours, and usually occurring during the night. In all other respects she is perfectly well.

ADDITIONAL NOTE.

Unfortunately in the stress and strain of a somewhat harassing case in the midst of a busy general practice complete daily notes of the blood pressure and amount of albumen were not preserved. It was however noted at the time, and the albumen steadily decreased after parturition and within a fortnight was only a trace. This persisted for another three weeks, then was only present intermittently and finally disappeared completely after some six weeks.

The blood pressure also fell steadily after parturition, and was within normal limits in ten days. Thereafter it rose slightly when activity was resumed, and then again returned to normal.

The oedema decreased rapidly after delivery and was gone by the seventh day of the puerperium; there was slight swelling of the feet when the patient walked about again but this also soon disappeared.

CASE 2. Mrs. B.

A healthy well nourished primigravida aged twenty-one years, seen for the first time in labour, as an emergency call from a midwife. Gestation had been uneventful and labour commenced during the night of February 21st 1936. Pains had been frequent but of short duration and ineffective, although causing much distress. Assistance was sought on account of the lack of progress after twenty-four hours.

When seen in the evening of February 22nd the patient was in an excitable state, and in much mental distress though the general physical condition was good. The os admitted two fingers, uterine contractions were irregular in time and very feeble. The presentation was a vertex, L.O.A., and no evidence of abnormality was detected. The foetal heart sounds were satisfactory. A diagnosis of Primary Uterine Inertia was made, and morphine gr. $\frac{1}{4}$ administered hypodermically.

Subsequently the uterine contractions ceased, and the patient slept for several hours. Contractions recurred at intervals throughout the following day (the second day of labour), but no progress was made. The patient took a little nourishment, mainly fluid but vomited after taking milk and thereafter took very little. The third day of labour brought an increase in the strength of the contractions and after a hot enema/

enema and catheterisation labour progressed slowly during the day, and by the evening the head was on the perineum. Contractions were now occurring regularly and frequently but the outlet was small and the patient could not deliver herself. Chloroform was administered and the delivery completed by application of low forceps, a first degree perineal tear being sutured.

Anaesthesia lasted some twenty minutes. The baby was healthy and living. The placenta was expressed immediately by Credes manipulation. The loss was within normal limits and nothing unusual was noted about the placenta. The total duration of labour was sixty-eight hours and during that time the patient took very little nourishment and a minimum of fluids. She had several hours sleep on the second night but apart from this had only very short interval of sleep during the three days.

At the end of labour the patient was very tired, but her general condition was fair considering the length of labour. She had a good night and on the following day, the first day of the puerperium, appeared much better. Her obstetrical condition was satisfactory, her pulse and temperature were normal, and after some persuasion she was able to take milk, gruel and other fluids. On this day she was also able to suckle the baby. There followed a very restless night and/

and when seen on the morning of the second day of the puerperium the patient was drowsy but rousable. She had vomited once, the vomitus being curdled milk. The pulse rate was accelerated, but no pyrexia was present. The blood pressure was normal. A catheter specimen of urine contained no albumen, bile or sugar. Four hours later, there was a trace of jaundice, drowsiness was increasing rapidly to the verge of coma, the pupils were dilated, reflexes were very brisk with a flexor plantar response, and the vomiting had become more severe, the vomitus now being black from altered blood. No alteration in liver dullness was detected. The patient was transferred to Queen Charlotte's Maternity Hospital, but the severity of the condition rapidly progressed, the pulse was rapid and feeble, and by the time she arrived in hospital she was deeply jaundiced and comatose. I am indebted to the Registrar of Queen Charlotte's Maternity Hospital for further details of this case, and for the post-mortem notes.

In hospital the cerebro-spinal fluid was found to be under pressure, but otherwise normal. A catheter specimen of urine showed albumen and acetone, no sugar and curiously, no bile. She was treated with intravenous saline and glucose but died within twelve hours of admission.

Post-Mortem/

POST-MORTEM REPORT.Whole body deeply jaundiced.Brain and meninges nothing abnormal.Heart normal, save for a few subepicardial haemorrhages.Lungs - general oedema.Stomach and jejunum contained altered blood. Remainder of gut normal.Liver - size about normal, weight 1375 grammes. Section showed widespread necrosis. In much of the liver almost the whole of each lobule was destroyed, with the exception of a narrow zone of cells round the portal canals.Kidneys - section showed some degeneration of the tubular epithelium.Spleen, pancreas and adrenals - nothing abnormal.Pelvic Organs - no abnormality.

The cause of death was said to be necrosis of the liver.

HISTORICAL.

The early history of the disease would seem to be enveloped in the uncertainty of long past years, though it is certain that the existence of such a condition was recognised and reported long before it received its present title of acute yellow atrophy of the liver in 1842. Thus various workers delving into the past have found references to such an illness, and the Paris physician Baillou who died in 1616 apparently first recorded two cases which appear to fit the clinical picture. Williams (3) in his textbook of Obstetrics cites Kirkring (1706) as being the first to describe a fatal case in pregnancy. Abercrombie in 1821 described a case very accurately under the name of "black ramollisment". Bright in a paper appearing in the first of Guy's Hospital Reports 1836 (4) on various types of Jaundice, describes the case of a woman who died "under the most urgent symptoms of jaundice" and whose liver was "rather small the lighter parts were of a brightish yellow colour and slightly raised above the surface the darker parts red and somewhat sunk". He also appends a drawing which might well be that of the liver of Acute Yellow Atrophy.

But to Rokitansky (5) goes the credit of placing the disease on a sound basis, for he gave a masterly description/

description of the pathological picture in 1842 and gave the disease its name. This classic description has never been bettered though our interpretation of it has undergone considerable modification. Since that time case records have slowly accumulated, and Thierfelder (6) in 1880 collected 200 cases and other notable collections of recorded cases have been made by Hunter, Best and Rolleston.

DEFINITION.

Acute yellow atrophy of the liver is a well defined anatomical condition, characterised by an acute necrosis of the parenchymal liver tissue with a marked diminution in size of the liver and associated with a grave clinical syndrome in which jaundice and severe nervous symptoms are a prominent feature, usually with a fatal termination.

Some confusion has arisen in regard to the name of the disease since it will be demonstrated that the present name is not terminologically exact. Thus the names, "acute necrosis", "acute autolysis" and many others have been suggested which would more accurately define the disease, but since the old title of acute yellow atrophy is universally used in the literature it will be maintained in this paper. The matter will be referred to again.

ETIOLOGY.

Our knowledge of the etiology of Acute Yellow Atrophy of the Liver is extremely limited, and beyond a few statistical facts and the recognised association of a variety of toxic substances with the majority of cases recorded we know nothing. In dealing with the etiology therefore I propose to present first, a summary of the statistical data culled from a study of the literature. Then discuss in turn each of the concomitant associated and possible predisposing factors, and finally examine from an etiological standpoint the new material presented in this paper with the aim of clarifying the position in this difficult matter.

INCIDENCE.

It is universally accepted that the disease is extremely rare, so rare in fact as to be almost a clinical curiosity, and many practitioners never meet with a case in the whole of their professional experience. Thayer (7) records that among 21,682 medical cases treated at the Johns Hopkins Hospital, Baltimore, up to 1908 there were only three cases of Acute Yellow Atrophy. Rolleston (8) quotes Turnbull's figures from the London Hospital, where in 12,449 necropsies performed between 1907 and 1920 there were 18 cases, of which amongst adults, nine were females and two males, seven cases were children below seven years of age.

Rolleston/

Rolleston also gives a table from the Registrar General's returns for the years 1913 to 1919 showing the deaths from Acute Yellow Atrophy in persons over fifteen years of age. The total number of deaths in the seven years was 363, an average of 51.8 deaths per year. Howard (9) in fifteen years work at University Hospital, State University of Iowa saw no cases in 13,205 medical cases, and only one case in twenty-five years hospital practice though this was followed by meeting three cases in fifteen months. He advances the belief that the condition has been more frequent during recent years, and states that in the fifteen years between 1911 and 1926 among 24,944 medical cases admitted to Montreal General Hospital, there were seven cases. He supports his belief by quoting figures from German authorities who have observed a definite increase in incidence since the Great War. The number of case reports published of such a rare disease is also a reflection of its incidence, although admittedly not necessarily a true reflection. Thus William Hunter (6) points out that in 1880 Thierfelder was able to collect only 200 recorded cases, by 1895 he himself was able to add another 50 cases, and Best in 1903 could muster no more than 500. From my own study of the literature of the past decade, I have found no evidence of an increased incidence/

incidence of the disease, other than references to the work of the German authorities quoted by Howard.

Certainly there has been no ^{general} increase large enough to be of any material significance.

INCIDENCE IN PREGNANCY.

Puerperal cases are included under this designation. It has been recognised for many years that the disease is more common in pregnancy, but absolute figures in this connection are difficult to obtain since the disease is not notifiable and records are often unreliable and difficult to trace. Hence estimates of the incidence are based largely on fatal cases, this error pertains to the general incidence also. On the other hand, this fallacy may be partially balanced by the non-inclusion of cases of the disease which are unrecognised as acute yellow atrophy or are classed under some other designation.

However, Hunter (6) cites in this connection Brauns figure of 1 in 28,000 pregnancies and Spaeths estimate of 2 in 33,000 pregnancies. Rolleston (8) quotes Thierfelder's table of 143 cases in which 30 occurred in pregnant women and another 3 cases in puerperal women. Stander (10) states that 60% of all cases of acute yellow atrophy occur in pregnant women. (Quincke).

The/

The generally accepted figure seems to be somewhat lower than this. In England and Wales during 1934 there were 6 cases of death from acute yellow atrophy (11) giving a rate of approximately 1 death from acute yellow atrophy per 26,000 confinements. In examining case reports from the Edinburgh Royal Maternity and Simpson Memorial Hospital I have found only three deaths recorded as due to acute yellow atrophy from 25,086 maternity cases treated between the years 1928 and 1934. In noting this latter figure it must also be noted that this is a hospital series of cases, in which one may expect to find a higher incidence since any series of hospital cases naturally tends to contain an abnormally high proportion of serious and complicated cases. But it serves to illustrate the rarity of the disease.

SEX AND AGE.

It is obvious from the foregoing statements that the sex incidence is predominately female. Osler (12) gives the proportion as two out of every three cases. Rolleston (8) believes it to be rather less, and states that in adults the proportion is nearly two to one. In children however, he points out that the incidence appears to be reversed, and cites Phillips (13) 34 cases of which 25 were male and only 9 female. Most authorities accept the proportion as being/

being two female cases to one male. Howard (9) and Hunter (6).

Similarly the effect of pregnancy is evident in the age incidence, since a greater number of cases occurs in the third decade than at any other age period. Hunter, Rolleston and Osler are in agreement that fifty per cent of cases occur between the ages of twenty and thirty. It appears however that no age is exempt, cases have been recorded in the first year of life and even at birth by Skormin (14) who collected seven such cases. It has also occurred up to the age of seventy.

PREDISPOSING FACTORS.

A. EXTRINSIC TOXINS.

It has long been recognised that acute yellow atrophy of the liver is frequently associated with a variety of poisons and toxic agents, both of an organic and inorganic nature. The following, although not necessarily a complete list, represents the principle agents which have been reported in this connection.

1. PHOSPHORUS.

Cases of phosphorus poisoning produce a clinical picture which is identical with that of acute yellow atrophy, and a number of cases have been described/

described (16) especially in Austria, where phosphorus was popular as an abortifacient and suicidal agent towards the end of last century. The two conditions appear to have been frequently confused by the earlier workers, but it has now been suggested that pathologically and chemically there are certain distinctions, certainly in the acutest cases. Thus Rolleston (17) points out the similarity of the clinical features but states that the liver may be and commonly is enlarged, and gives the progressively diminishing size of the organ in acute yellow atrophy as a differential diagnostic point since the two conditions differ pathologically except in rare cases when atrophy may occur. McCallum (15) emphasises the prominence of fatty changes in phosphorus and all poisoning cases.

Histologically it has been shown that the cells of the peripheral zone of the lobules are always initially and most severely affected in phosphorus poisoning, and that in the individual cells the cytoplasm appears to be affected primarily whereas in acute yellow atrophy it is the nuclei which bear the brunt of the injury (18). Chemical studies have suggested that the proportion of fat is considerably increased in the liver in phosphorus poisoning whereas in acute yellow atrophy it is diminished. These findings are not universally accepted, some of the German authorities deny that there is any essential difference between/

between the atrophy of phosphorus poisoning and acute yellow atrophy. Certain it is that some cases remain in which the liver is reduced and closely resembles the liver of acute yellow atrophy. Most fatal cases of phosphorus poisoning die fairly quickly and the small liver is usually seen in cases which have survived some time and represents a more advanced stage of poisoning.

Sufficient has been said to illustrate the marked resemblance of the two conditions.

2. CHLOROFORM.

The similarity both clinically and pathologically, between the effects of chloroform as seen in delayed chloroform poisoning and acute yellow atrophy is very striking. Indeed the diagnosis between the two is sometimes impossible, and even after death when pathological material is available the final differentiation may be inclusive. This is well exemplified by Case II in this series, and the point will be discussed later, (Vide Infra - Diagnosis). Rolleston (17) describes two forms which the toxic effects of chloroform may take:-

1. An acid intoxication with no jaundice and with fatty change distributed in the periphery of the liver lobules.

2. Resembling acute yellow atrophy.

The/

The latter form he declares, is rare, and requires additional factors to explain its occurrence. He suggests diminished liver cell resistance and infection as being the possible additional factors. It is with the latter form we are concerned. McCallum (15) sums up the histological changes in the liver as being a necrosis and fatty degeneration, particularly affecting the cells of the central zone of the lobules. The nuclei of the liver cells are non-staining, whilst the cell body is coagulated and deeply staining with eosin. There is an accumulation of fat in the organ although this does not seem to be as marked as in phosphorus poisoning.

These changes have been confirmed by many workers, amongst whom Whipple and Sperry (19) have furnished experimental proof of the occurrence of liver cell damage after the administration of chloroform. They believe that this occurs constantly when chloroform is used as an anaesthetic, and have shown that in dogs recovery even from severe damage may take place rapidly. They showed also that the same changes take place in pregnant and non-pregnant dogs, and that the changes are extensive central necrosis and fatty degeneration in the liver, with fatty degeneration of the heart and kidneys, sometimes fat necrosis in the pancreas and maybe haemorrhages and ecchymoses in the peritoneum or upper/

upper intestinal tract. They record a fatal case in man of almost complete liver necrosis after a single administration of chloroform for thirty-five minutes. Opies work (20) is in agreement with these findings in that chloroform may produce necrosis and fatty degeneration, stating that the change is seen in the central two-fifths of the lobule and he believes that fatty degeneration occurs where the chloroform is not sufficient to produce death of the cells. The chemical studies of Wells have served to emphasise the similarity between certain cases of delayed chloroform poisoning and acute yellow atrophy (21).

As in phosphorus poisoning, death in cases of chloroform poisoning occurs quickly, usually within three to five days, and the longer the patient has survived the more nearly do the changes in the liver approach those of acute yellow atrophy. It seems abundantly clear then that chloroform is an agent which is capable of producing a condition identical with that seen in acute yellow atrophy.

3. MUSHROOM POISONING.

Certain varieties of mushrooms have been reported as causing an acute necrotic process in the liver, though the clinical picture of the illness is not strictly analogous to that of acute yellow atrophy and pathologically, whilst the liver appearances/

appearances resemble closely acute yellow atrophy, distinguishing features occur in other organs. (Ford 22)

4. TRINITROTOLUENE AND TRICHLORETHANE.

During the Great War a number of cases of poisoning occurred in munition and aeroplane workers. Spilsbury (23) and Turnbull (24) have reported many of these cases and stress the finding of a liver necrosis like that of acute yellow atrophy as the main pathological feature of the disease. Their work has been confirmed by others, and clinically the two diseases are similar in the manifestations of jaundice, vomiting and profound nervous disturbances.

5. ARSENIC.

From time to time cases have been cited of arsenical compounds, usually of the organic type, causing or being associated with a true variety of acute yellow atrophy. McDonald (25) thus reports five cases of acute yellow atrophy in cases of syphilis all of whom had received a full course of Salvarsan injections. He suggests that in view of the large number of syphilitic cases treated by Arsenical compounds, the rarity of the complication must be due to the presence in such cases of a determining factor. Numerous other reports have been published confirming the association of acute yellow atrophy and arsenical poisoning, and/

and most authorities accept the association. (Rolleston and McNee (8), Hunter (26), Osler (12)).

6. CINCHOPHEN AND ITS DERIVATIVES.

A large number of proprietary drugs containing cinchophen are available, - Atophan, Quinophan, atophanyl and Novatopin to mention only a few. From time to time cases of acute yellow atrophy have been reported in which there was a history of such drugs having been taken. Cabot and Painter (27) have produced a series of cases in which they believe Cinchopen was the causal agent. Lehman and Hanzlik (28) however were unable to demonstrate an experimental basis for the direct relation of cause and effect, in their work with rats and rabbits. Moreover they showed that previous damage to the liver by chloroform and phosphorus did not predispose to toxic effects from cinchophen administration. But they came to the conclusion that the drug possessed harmful potentialities, and should be used with caution, especially in cases with pre-existing hepatic disease or injury. On the other hand Permar and Goering (29) examining two cases clinically, pathologically and histologically came to the conclusion that cinchophen intoxication causes hepatic damage which is essentially the same as that of acute and subacute atrophy, involving primarily the central/

central zones of the lobules. They also pointed out that an acute gastro-intestinal lesion might accompany the necrosis in the liver.

7. ALCOHOL.

Most of the text books mention alcohol as being one of the predisposing causes of acute yellow atrophy, and in the light of our knowledge of alcoholism and its effects on the liver it must be borne in mind as a factor. But I have been struck by the conspicuous absence of evidence of alcohol playing any part in the etiology in the vast majority of recorded cases. Thus Rolleston (8) records the only case I have found in which alcohol might be assumed to have played a leading part. Therefore on the present evidence one cannot accept the role of alcohol in acute yellow atrophy of the liver as anything more than the subsidiary one of an agent lowering the general resistance of the organism.

8. OTHER HEPATIC POISONS.

It is unnecessary to consider in detail all the many other poisonous substances which have been reported in connection with acute yellow atrophy. Suffice it to add that Price (30) mentions the following as being the chief among these Avertin, Carbon tetrachloride/

tetrachloride, arseniuretted hydrogen, gold, acetanalide, aniline, santonin, felix mas, and snake venom.

B. BACTERIAL INFECTIONS.

1. SYPHILIS.

It has long been known that many cases of acute yellow atrophy are associated with spirochaetal infection, and many of the earliest cases described were attributed to this cause. Much discussion has taken place as to the nature of the association between the two conditions, some regarding syphilis as the causal agent, others believing that therapeutic agents such as mercury and arsenic are the activating cause, rather than the specific infection per se. Yet a third school of thought suggests that both may be only pre-disposing factors and that the onset of acute yellow atrophy is determined by an additional factor, secondary bacterial infection being the factor usually implicated. This controversy though not yet settled, scarcely concerns us here, the important point being to emphasise the occurrence of syphilitic infection in too great a number of cases of acute yellow atrophy to be entirely fortuitous. Weber (31) in a survey of the situation has produced abundant evidence to confirm this point, which is now accepted by most workers.

2. INFLUENZA.

Miller and Hayes (32) in 1909 published a paper in which they pointed out the possible association of influenzal infection with acute yellow atrophy, and produced evidence in support of their contention. Since that time other cases have been brought forward in which acute yellow atrophy occurred during or following an attack of influenza. Roxburgh's (33) case is an interesting example. Rolleston (8) in this connection cites the records of the Mayo Clinic showing increased incidence of liver complications between 1918-20, the alleged cause being the influenza pandemic of 1917-18.

3. INFECTIOUS OR EPIDEMIC JAUNDICE.

This also is a time honoured source of speculation with regard to acute yellow atrophy, and William Hunter in his section on the subject in Allbutt's System of Medicine (26) speaks of the outbreak of jaundice in Saxony and Dresden in 1889. In this epidemic there were 518 cases, the disease was characterised by two stages, an initial febrile period with headache and vomiting, rigor but no jaundice, and a second stage of jaundice without fever. Thirteen cases died, and two of them had all the symptoms of acute yellow atrophy.

In/

In more recent times epidemics of unexplained jaundice have occurred. In America in 1921-22 widespread epidemics occurred for which no cause was found (34) and Roman (18) noticed that between 1921-1923 seven cases of acute yellow atrophy were found at post-mortem as against no cases in the previous few years. He believes on these grounds and the evidence of German workers, that epidemic jaundice has an etiological relationship to acute yellow atrophy, and that acute yellow atrophy may arise from epidemic jaundice.

4. OTHER BACTERIAL DISEASES.

Amongst other bacterial infections in which acute yellow atrophy has been recorded are osteomyelitis, erysipelas, salpingitis, sepsis, gonorrhoea, typhoid fever, pneumonia, diphtheria and appendicitis (recorded by German workers cited by Roman (18)). Miller and Rutherford (35) in an analysis of collected cases, found post-mortem evidence or history of tuberculosis in 10 out of 16 cases, syphilis in 2 cases and possibly 2 others, enteric fever in one case, scarlet fever in one case as a terminal complication and 2 cases gave a history of scarlet fever. Stuart McDonald (25) isolated an organism resembling the coli-typhoid group from the heart and blood in all of his five cases. Finally the work of Opie (20) demonstrated that changes identical/

identical to those seen in the liver in acute yellow atrophy could be produced by the injection of Bacillus Coli and the administration of chloroform, though neither agent would produce the change by itself. He further showed that a hepatic poison was able to produce its effects in smaller doses when bacterial infection was present. He came to the conclusion however that "the infrequency of the lesion and the frequency of bacterial infection indicate that the association of some undetermined factor, perhaps some disturbance of metabolism, is essential for its production". His results await confirmation.

C. OTHER ETIOLOGICAL FACTORS.

1. MENTAL DISTURBANCE.

Hunter (26) mentions the possibility that fright or associated depressing emotion may be the precipitating cause of acute yellow atrophy and states that Haywood in 1890 went so far as to suggest that the disease is primarily a nervous disorder. He produces no evidence in support of this statement. Rolleston on the other hand also remarks that French and German workers have produced cases illustrating the onset of acute yellow atrophy after a severe shock or fright - he himself inclines to support the view. No other evidence has been found on this point.

2. PRE-EXISTING LIVER DISEASE.

That this may be a predisposing cause to a disease in which manifestly the liver bears the brunt of the injury would seem self-evident. Yet it appears to play very little part in the incidence of acute yellow atrophy, for it is very rarely that the presence of previous liver insufficiency is demonstrable. Remarkably few of the recorded cases display any such feature, but the point has been made by Hunter (26) and Osler (12).

3. TOXAEMIAS OF PREGNANCY.

In examining post-mortem reports from fatal cases of eclampsia and severe toxæmias of pregnancy one cannot fail to be struck, as I have been, by the frequency of the occurrence of necrosis of the liver. The necrosis is often widespread throughout the organ, sometimes scattered and frequently the liver is shrunken and yellow. Microscopic sections reveal that the necrosis is zonal in distribution, and I have found cases in which the zonal necrosis is stated to be central in one area and peripheral in other areas of the same organ. (35) The similarity in the clinical picture is no less striking.

It is generally accepted that necrosis of the liver is a feature of the pathology of eclampsia, though on the character of the necrosis there is divergence/

divergence of opinion, the view of the majority being that the necrosis is in the peripheral zone. McCallum (15) stresses this point of distinction between the two conditions. Williams (37) in a discussion on the toxæmic vomiting of pregnancy reports several cases in which the end stage was a typical clinical and pathological picture of acute yellow atrophy. He insists however on the distinction between toxæmic vomiting of pregnancy and acute yellow atrophy on the one hand and pre-eclamptic toxæmia and eclampsia on the other. He justifies this distinction on clinical, chemical and pathological grounds. Case 1 in this series is of considerable interest from this point of view, since the acute yellow atrophy followed after a period of pre-eclamptic toxæmia. The main fact emerges that the toxæmias of pregnancy are sometimes associated with acute yellow atrophy.

COMMENT.

It is appreciated that in discussing etiology with two or even a number of cases of the disease as a basis no general conclusions as to causation can be arrived at - but if this fallacy is remembered considerable light may be thrown on the subject by a detailed consideration of only one case. It has been seen from the/

the foregoing description that acute yellow atrophy is not a clinical entity, and as Wood (38) has noted "it is probably erroneous to consider the lesions of the liver described as acute yellow atrophy as marking a single disease process." It may arise under a variety of different circumstances and with a number of associated factors - but no single one of which seems to fit the role of a constant common causal agent. Indeed it is necessary to point out that although the enumerated predisposing causes are frequently found in cases of the disease, yet there still remains a considerable number of examples where none of these factors are noted - the so-called idiopathic cases in which the causal agent is quite unknown. The disease is an end product which may be arrived at by a number of different routes, though it is obvious that these cases must have some common underlying factor. It has been generally assumed from analogy that this common factor is a toxin, which in the idiopathic cases has so far escaped detection. It seems to be a reasonable though not necessarily correct assumption in view of the profound intoxication evident clinically and the fact that we know that poisons can and do cause acute yellow atrophy. Whilst accepting this I believe that a truer appreciation of the condition is obtained by regarding the disease from another angle.

Taking the essential fundamental feature of the disease,/

disease, common to all types however produced, we have necrosis of liver cells. This is undoubtedly the outstanding feature (vide infra Pathology.). Now from our knowledge of physiology and cell metabolism we know that cell death will follow from any of the following causes or from a combination of these causes even in slight degree.

1. The deprivation of water.
2. The deprivation of Oxygen.
3. The deprivation of food, or of certain essential elements of nutrition.
4. The failure to remove waste products.
5. Failure of the controlling force, which may be hormonal, nervous, enzymic or a combination of these, and about which we know little.

The presence of a protoplasmic poison presumably acts by interfering with one or more of these factors. From this it follows that a poison or toxin will act more readily if one or more of these essentials of cell life is interfered with, moreover if such interference is already present substances which are normally non toxic may become potentially toxic. In other words, it is suggested that the common feature underlying all cases is fundamentally a disturbance of cell metabolism. That this affects only, or primarily liver tissue is due to the fact that the metabolic change or disturbance is localised to liver cells. Furthermore since cell metabolism is admittedly a complex mechanism, which/

which may be disturbed in a variety of different ways, it is to be expected that different disturbing agents producing their effect in different ways will produce the same essential end product, but with minor individual distinctions. This is no new conception. Opie in his work (vide supra) accepted the possibility and other workers, notably Miller, Rutherford (35) and Wood (38) have taken this viewpoint. Furthermore there is some evidence pointing to a disturbance of carbohydrate metabolism as being this theoretical metabolic disturbance.

Taking Case 1 of this series. The outstanding feature, but quite a common feature in studying case histories, is the number of possible options. We have the association of pregnancy; administration of a hepatic poison (chloroform); the presence of a mild chronic infection (the naso-pharyngeal catarrh); the existence of pre-eclamptic toxæmia and a previous history of pre-eclamptic toxæmia which might have left a permanent slight impairment of liver function; lastly there is the past history of infections in the early years of life.

In Case 2 we have pregnancy and chloroform to consider. There may have been other factors in this case also, since I have no record of this patient's earlier history. In neither case was there evidence of syphilis, and although no Wassermann reaction was obtained/

obtained, there can be no doubt certainly in case 1 that it was not present.

Chloroform - the question of diagnosis arises here since it might be argued that these cases, especially Case 2, were cases of delayed chloroform poisoning and not acute yellow atrophy. But as I have tried to show in the foregoing the results of chloroform poisoning are in many cases, and especially those cases which have survived for some time, indistinguishable from those of acute yellow atrophy. Undoubtedly in certain cases delayed chloroform poisoning is acute yellow atrophy, although obviously the converse is not true. I believe that in Case 2 chloroform did play a very great part, and was in fact the main etiological factor in the production of the disease, assisted and preceded by other factors which I shall refer to later. In Case 1 on the other hand chloroform probably also played a part, but in this case we know from the patient's previous history that chloroform had been administered at least three times previously without the sequelae of the hepatic syndrome. Moreover on at least one occasion, it was given in much greater amount, at the tonsil operation where I myself administered it. It is significant however that this was followed by persistent vomiting, which I believe in the light of subsequent events to have been due to an existing lowered/

lowered hepatic resistance. On the other two occasions when chloroform was given, pre-eclamptic toxæmia was present also, yet again no hepatic syndrome followed. It seems abundantly clear from this that another factor than chloroform, even combined with pre-eclamptic toxæmia was necessary for the production of acute yellow atrophy.

Association with Pregnancy. It has already been shown that most cases of acute yellow atrophy do occur in pregnancy, or its allied puerperal state, but one other feature requires emphasis. It has been found that in pregnancy - acute yellow atrophy tends to occur at three periods:-

- (a) In the early weeks (Roman records a case at the fifth week (18).
- (b) In the second half of pregnancy, and usually after the seventh month (8) (26).
- (c) In the first few days of the puerperium. (12)

This is significant in that it is at these periods we should expect to find the disease if its onset is influenced by metabolic disturbances, or decreased hepatic function. These are the times at which the greatest modifications in metabolism are taking place. Furthermore since the time when Hofbauer called attention to "the liver of pregnancy", evidence has been forthcoming that there are marked changes in the liver during the last few months of pregnancy. These include the disappearance of glycogen from the central portion/

portion of the liver lobule, passive congestion of the central veins, stagnation of bile in the biliary channels, a decrease in the glycogen content of the liver as a whole and above all a definite impairment of liver function. (Curtis, Schmidt, Kaufmann (39)). Titus and Dodds (40) have also produced convincing evidence of the existence of a disturbed carbohydrate metabolism in the toxaemias of pregnancy, and came to the conclusion that the difference between hepatic states in the various toxaemias of pregnancy is not so marked as is generally supposed. Thus it seems that certainly in pregnancy, there is evidence to support the theory that the onset of acute yellow atrophy has as its basis a metabolic disturbance. I can produce no evidence in support of the application of this theory to acute yellow atrophy of the liver occurring apart from pregnancy, but in the idiopathic cases could it not be the missing link in the etiology?

Next with regard to the presence of an infection. In Case 2 there was no evidence of any such infection being present, but in Case 1 a chronic bacterial infection did exist. This must be accepted as tending to lower the general resistance of the patient, and may even have played a greater part if one accepts Opie's work on the combination of bacterial infection with chloroform administration. On the other hand the afebrile/

afebrile nature of the illness is not in keeping with the effects customarily attendant on a bacterial infection, and my own belief is that it only played the subsidiary role first mentioned. Again in Case 1 previous bacterial infections are known to have occurred, but how far the patients earlier illnesses of scarlet fever, summer diarrhoea and measles may have predisposed the liver to necrotic agencies or metabolic dysfunction it is quite impossible to estimate. The frequency with which bacterial infection is an antecedent in any disease precludes the possibility of this factor being regarded any more than speculatively.

So much for the accepted influencing factors. Are there any other circumstances in these cases, having a bearing on the etiology? Both cases have this feature in common - in the period immediately prior to the onset of the hepatic complication, neither of the patients received much food, and their intake of fluid was minimal. Also, and this is especially true in Case 2, the amount of sleep obtained in the previous seventy-two hours was considerably less than the normal requirements. Since the metabolic requirements in conscious hours are considerably greater than in sleep, these two patients' lack of sleep must have lessened an already deficient supply of nourishment and fluid. This was further diminished by the increased/

yet is it not possible that a congenital or innate predisposition to hepatic dysfunction might be a feature of acute yellow atrophy? Whilst not wishing to labour this point it is possible that a careful case history of idiopathic (and other) cases might reveal something of this nature.

Nothing has been said of the possible part played by hormones in this condition for until recently there has been no evidence in either direction. The recent work of Hall and Korenchevsky (41) on the effect of sex hormones on liver changes in rats is interesting in this respect, for it suggests that the growth and development of the liver is intimately associated with hormonal balance. The implications of these facts if confirmed need no further emphasis after what has already been said about cell metabolism.

To sum up, it is believed that in the cases here recorded a combination of a cell poison and a metabolic disturbance from a variety of causes are the essential features of the etiology. Furthermore it is suggested that acute yellow atrophy of the liver is the result not of one single etiological factor, but of a combination of a number of factors influencing liver cell metabolism.

PATHOLOGY.

Controversy is as the breath of life to the Pathologist and though Acute Yellow Atrophy of the Liver affords him abundant scope for his imagination in relation to the mechanism by which the observed changes take place, yet certain striking facts emerge from a study of the morbid anatomy and pathology of the condition to which general acceptance is given.

Thus Wood (58) summarises the disease as "characterised by a rapid diminution in size of the liver as the result of granular and fatty degeneration, necrosis and disintegration of liver cells". This decrease in size is a fairly constant and marked feature. Variations occur in the degree of diminution of size, but it is usual to find that the organ is only one half to one quarter the normal size. Frequently at autopsy the shrivelled viscus is found lying high up, fallen away from the ribs and tucked up under the diaphragm and not uncommonly overlain by coils of intestine. This latter feature accounting for the tympanitic percussion note observed clinically over the normal area of liver dullness. Similarly it may be noticed that for this reason the apparent clinical diminution in size of the liver is not a true index of the actual decrease in size. It is fair to add that some of the earliest descriptions of the macroscopic findings, suggested that an initial increase in size occurred/

occurred to be rapidly followed by a decrease. Most of the recent descriptions do not support this view, and it has been suggested that in such cases a previous pathological enlargement masks the true appearance. But Roman (18) in his admirable survey of the pathology of Acute Yellow Atrophy believes that cases with initial enlargement do occur. The liver then is usually diminished, especially in its vertical diameter, the anterior border is sharp and though the change is general to the whole organ, the left lobe is often decreased to a greater extent than the right. The consistence is soft, and the tissue is readily cut by the knife. The capsule as would be expected under the circumstances is markedly wrinkled and the colour of the organ is altered. This alteration is variable, depending on the stage at which the liver is seen, and the length of time that has elapsed from the onset of the disease. Hence we find an opaque ochre yellow as a background with interspersed reddish or greyish areas, or red may predominate. Further Karsner (42) points out that after exposure to air for a few hours, the yellow colour may give place to green, due to the alteration of bile pigment on exposure to oxygen. Combinations of these colours may be present in the same liver, and on section a mottled arrangement of red and yellow is seen on the cut surface, the early cases/

cases showing a predominance of yellow, the later specimens a predominance of red or greyish red. A variety of stages may be seen in different areas. The cut surface also reveals that the normal lobulated structure of liver tissue is conspicuously absent, and an irregular bulging is noticeable the yellow areas being prominent, soft and friable, almost mushy, whilst the red areas in contrast are sunken and though flabby are more resistant. Crystals of leucin and tyrosin may sometimes be found on the surface.

With improvement in laboratory technique, the association of case history and morbid anatomical findings, and the accumulation of material it has been possible to correlate the variety of appearance found at autopsy. It is appreciated that pure yellow atrophy (in a morbid anatomical sense) is rare and represents the earliest stage of the disease process; a widespread necrosis of parenchymal tissue, the immediate effect of the first onslaught of the disease. This was the stage first described by Rokitansky in 1842 (5) and from whence the nomenclature arose.

As more cases were described it was recognised that the superimposition of red areas represented a more advanced stage of the same condition, and the red areas corresponded to areas where a scavenging process had occurred and the necrotic resultant tissue of the primary injury had been removed. These appearances then/

then are to be found in cases where life is prolonged for a sufficient length of time for the liver tissue to react to the injury and are generally regarded as a subacute stage.

A chronic phase may supervene and Roman (18) credits Marchand 1895 as being the first investigator to recognise that in a case of his which survived for six months; multiple areas of nodular hyperplasia were present, evidence of the reparative activity of the liver, and occurring where the reparative process tends to dominate the destructive process. In this stage a condition not unlike cirrhosis may be produced and MacDonald & Milne (43) quote a case in which nodules of hyperplasia were conspicuously present and assumed a form reminiscent of polypus projecting from the liver. Roman (18) supports these findings from his own experience and emphasises the similarity of the appearance at this stage to that of a diffuse cirrhosis of the liver. Such changes in their earliest form are represented by the grey areas seen in the liver.

Since these different stages may occur side by side we have a satisfactory explanation of the variety of macroscopic findings.

The gall bladder is usually found to be relaxed and may be empty or may contain bile. The bile if present is commonly of a thin or slightly viscid nature, sometimes/

sometimes light, occasionally though rarely dark in colour. It is usual to find the common bile duct patent and empty and the larger bile ducts are also empty.

HISTOLOGY (MORBID).

In discussing the macroscopic appearances I have already indicated the thre^Afold nature of the changes found in the liver tissue, but more detailed description is necessary and some further points need emphasis. L e

The most striking feature of microscopic sections is the widespread nature of the condition and its severity. I have examined numerous sections from cases of Acute Yellow Atrophy both from different cases and different sections from the same liver, and I have not been able in any section to find an area in which the liver cells had a normal appearance.

Taking the parenchymal tissue first - all stages of liver cells can be found from slightly swollen hazy looking cells to the last detectable stage preceding complete destruction. The earliest change observed is cloudy swelling of the liver cells -, others show fatty degeneration, some a hyaline and some a granular cytoplasmic structure. The nuclei are in the main poorly staining and some are so faint as to be almost un-discernible/

undiscernible.

Different appearances are found in different areas - but all areas have in common a striking decrease in the number of liver cells present. Some areas show a complete absence of parenchymal cells - being occupied by an amorphous hyaline or granular material, interspersed with cell debris, pigment granules, blood pigment, fat globules, occasional crystals and in some parts with cellular infiltration. Other parts may show numbers of liver cells in varying stages of disintegration and degeneration, mostly well separated from each other, and yet other areas may show a few isolated liver cells surrounded by a matrix of necrotic and granular detritus. Finally it is usually easy to distinguish, especially in more subacute types - areas where new liver cells are apparently in the process of formation.

Some of the latter appear as multinucleated cell structures with clear and swollen cytoplasm, some in what appears to be intimate relation to bile canaliculi, and some in association with surviving liver cells. Their origin is a fruitful subject of pathological polemics, a dual origin being sponsored by some authorities whilst other workers do not accept the bile duct origin of new liver cells as a proven fact. The point scarcely concerns us here - the important feature from the clinical standpoint being that liver cell/

cell regeneration does occur and to a remarkable degree. On this there is universal agreement (Roman (18)) and recovery and survival of the individual is therefore a possibility even after severe liver injury.

Of the non liver cells seen in the tissue there are three main types. First there are large mononuclear cells of phagocytic type - often distended and loaded with particles of debris. These are found scattered throughout the liver tissue but especially where the destruction of liver cells is most marked. Secondly there are both scattered and aggregate infiltrations of cells of the small round type, along with some leucocytes. The aggregations are especially found in the neighbourhood of the frontal spaces. Erythrocytes are also seen. Thirdly there are numerous proliferating connective tissue cells - well staining and with elongate nuclei. This latter is a pronounced feature and by the use of Mallory's stain a marked increase of fibrous tissue throughout the liver can be readily demonstrated in sections. Proliferation of capillaries has also been demonstrated. (Miller & Rutherford (35)).

Finally the small bile ducts are present in sections and the endothelium of the bile sinusoids and the Kupffer's cells appear to have escaped the wholesale destruction of cellular life evident throughout the organ. (McCallum)

Reference/

Reference to the topographical distribution of the changes described has so far been deliberately avoided, but so much has been written on the so-called zonal distribution of the pathological processes within the liver lobules that the subject would not be complete without some discussion of the point. Moreover it is of some significance, though beset with considerable difficulties in interpretation and appreciation. Indeed the existence of a zonal distribution has been denied by some workers. This view can scarcely be accepted since so many authorities working quite independently have described this appearance - although opinions have differed considerably as to which is the affected zone. From my own observations of sections I am in agreement with those who claim a zonal distribution, though it must be again emphasised that the pathological process is widespread throughout the parenchyma, and that the differentiation into zones is in fact one of degree of severity of affliction of the cells rather than one of absolute immunity of some cells. As has been pointed out in all the sections I examined, no unaffected liver cells were seen. (This I need scarcely add does not mean that no cells escape.) Frequently areas were found where a completely disintegrated area was surrounded by liver cells of varying degrees of degeneration, the cells furthest/

furthest from the necrotic area being least affected. This suggests a central zone affection of the lobule, though the normal lobular arrangement was not discernible with any precision on account of the severity of the changes. Competent authorities however have described the changes as affecting particular zones of the lobules more than others, and it is therefore a justifiable assumption that the changes commence first in these zones.

Disagreement however arises as to which is the zone showing the most advanced changes. Thus one school of thought brings evidence to bear that the change is most advanced and therefore commences first in the peripheral zone of the lobule, a second school of thought describes the changes as central and yet a third describes ~~xxx~~ mid-zonal necrosis as the characteristic feature.

At first sight it would seem that these views are irreconcilable, but it has been suggested that the zone of necrosis is not constant and varies in different cases. This latter view appears sound to me and receives considerable support from other sources. Thus McCallum (15) has suggested that the cells along those capillaries which take a tortuous course and hence a long time to reach the efferent vein, suffer at an equidistance from the portal vein, but not equidistant from/

from the efferent vein. If then in some liver lobules a short course is taken by the capillaries, in others a long course, an obvious variation in the pathological picture will occur.

Again it is stated by Karsner (42) that in prolonged hyperaemia the cells of the central zone are often necrosed, a variable factor which may thus influence the pathological picture. There are many such variable factors which may serve to determine the site of the pathological process; relative capacity of resistance of the liver cells, variation in oxygenation, amount of glycogen content and concentration of a toxic agency, to mention only a few.

The consensus of opinion seems to favour the finding of central zone necrosis as a characteristic of acute yellow atrophy. Therefore whilst it may be accepted that many cases of acute yellow atrophy will show a central necrosis, yet necrosis in other zones may equally well predominate, and that extreme caution is required in estimating the implications of the distributions, since the appreciated controlling factors are numerous and there are almost certainly other significant factors of whose nature we know nothing.

Whilst these changes are the essential feature of the pathology of acute yellow atrophy of the liver - the other organs of the body show changes though of an/

an entirely different nature. The whole body may be jaundiced and is so as a rule, though cases do occur where jaundice is not a feature of the clinical picture and is not found at autopsy. A common finding also is that of scattered haemorrhages in the cutaneous mucous or serous surfaces - petechial or purpuric in character, occasionally ecchymoses.

The Spleen is soft and enlarged, this enlargement being sometimes demonstrable in life. The enlargement is due to stasis in the portal circulation and accumulation of red blood cells and haemosiderin within the splenic tissue. Some of the German workers cited by Roman suggest that the spleen is also enlarged from the effect of the same etiological factor producing the primary liver changes. However examination of sections of the spleen microscopically fail to reveal evidence of tissue necrosis, the organs appear normal in structure and the cells appear healthy, the only abnormality being a marked crowding of red blood cells into the splenic capillaries.

The Kidneys are described by most authors as being enlarged and softened. The tissue is usually bile stained and haemorrhages may be present focally. On microscopic section there is seen to be diffuse degeneration of the parenchyma especially affecting the epithelium of the renal tubules, which show cloudy swelling/

swelling and fatty degeneration. The glomeruli are also affected but not so markedly as the tubules. Rolleston (8) records Hewitt as reporting five cases in which he found necrosis of the renal epithelium, but this does not appear to be a common finding.

The Heart is soft, swollen and pale, and there is always some degree of fatty degeneration marked in some cases.

The Brain and Central Nervous System - the severity of the nervous manifestations of acute yellow atrophy is not reflected in the morbid anatomical findings. I have been unable to find a detailed account of the brain pathology in this disease, most authors dismissing the nervous system in the brief sentence "degeneration of the tissue found". Rolleston (8) states that there may be haemorrhages on the surface of the brain or in the substance and Osler (12) records degeneration of the spinal cord.

Bone Marrow - shows hyperplasia usually accepted as the resultant of excessive blood destruction.

Gastro-intestinal Tract - may show haemorrhages or small areas of necrosis in the mucous membrane. This is not constant in all cases, catarrhal inflammatory changes being frequently seen. The lumen frequently contains altered blood.

The Pancreas also shows degenerative changes and foci of fat necrosis have been described by German workers. Finally ascites may be present in cases which have survived for some weeks - the fluid in such cases being bile stained.

COMMENT.

The morbid anatomical and histological appearances of Acute Yellow Atrophy have been described in some detail, primarily because they are necessary for a proper appreciation of the disease. Secondly considered broadly all disease is the resultant of injury to the living organism and the reaction of the organism to that injury, and in our search for the causes of disease we are given the end product and faced with the prospect of working backwards, through the varied and numerous stages of its development, till we reach the source of the original injury and can conceive of its nature and the conditions under which it was able to produce its injurious effects.

Thus Acute Yellow Atrophy of the Liver was the highly descriptive name first given to the disease in which the earlier observers found a clinical picture of a very fatal general illness with jaundice and nervous symptoms associated with the finding at autopsy of a small, much diminished, brightly coloured liver.

As/

As I have endeavoured to show in the foregoing description, further study of the disease has shown us that the name is misleading - since it is not an atrophy in the true sense of the term, nor is it necessarily yellow, not^d lastly is it always acute since variations of the pathological findings can only be satisfactorily classified under the subdivisions of acute, subacute and chronic.

It has been demonstrated that the characteristic feature of the condition is death of the liver cells - a necrosis, and we must regard the disease as one in which wholesale and rapid death of the majority of liver cells takes place. This is remarkable - when compared with the pathological processes and end results of other diseases. To quote Roman (18) we have "a picture that is unique in pathology - nothing similar occurring in any other organ", unique both as to its actual effect, since in no other disease do we find an organ the seat of such universal and complete destruction, and as to its localisation. For it seems a reasonable assumption that the liver is primarily affected, and that the pathological effects noticed in other organs is secondary and consequent upon the failure of liver function. This is the accepted view and considering the similarity of the lesions in all other organs, their nature and relative insignificance

I/

I believe it to be the correct interpretation of the facts.

With regard to the sequence of events in the liver itself it has already been stressed that three stages of the process are recognised - destruction, removal of the dead tissue, and regeneration - and that the various stages can and do coexist. One further point in this connection needs elucidation, the removal of the dead tissue. There is now an overwhelming accumulation of evidence that this is largely a process of autolysis, and not a phagocytic phenomenon though the latter also plays a part. Liver tissue removed from the body under sterile conditions has been found to undergo autolysis, and chemical analysis of the liver, blood and urine have furnished evidence in support of the contention. It is of course necessary in accepting this explanation, to assume that the factor causing the initial death of the liver cells does not at the same time destroy the ferments present in the liver.

The mechanism of the causation of the jaundice in acute yellow atrophy has received considerable attention. The earlier view of Hunter (26) and others was that the jaundice was obstructive in type due to occlusion of the smaller bile ducts by swelling of the lining cells from the action of the same etiological factor causing liver cell necrosis. This view is not now upheld, the jaundice/

jaundice being classed as a toxic jaundice by Rolleston and McNee (8) and regarded as due to functional failure of the liver cells. Bile pigment is now believed to be formed largely by the cells of the reticulo-endothelial system, and in acute yellow atrophy the liver cells being damaged and destroyed, the bile pigment is directly absorbed into the blood stream.

Thus it is shown that acute yellow atrophy is a striking pathological study, and a remarkable morbid anatomical entity. The post-mortem report appended along with Case 2 of this series is unfortunately lacking in detail, and no microscopic sections were available. In general features however, it fits fairly accurately the description of acute yellow atrophy. The liver however was not diminished in size, though it has been seen (*vide supra*) that some authorities believe a normally sized liver may be found in early stages, and it is to be noted that this patient died within twenty-four hours of the onset of symptoms. It is admitted that the pathological appearances could equally well fit the clinical diagnosis of delayed chloroform poisoning.

DIAGNOSIS.

The clinical diagnosis of acute yellow atrophy of the liver rests on the following points:-

1. History - onset and course.
2. Jaundice.
3. Nervous symptoms.
4. Vomiting.
5. Physical signs - (a. Liver dullness.
 (b. The Urine.
 (c. The blood chemistry.

THE HISTORY - is of obvious importance with regard to exposure to potentially toxic substances like phosphorus, chloroform or trinitrotoluene, or the taking of drugs likely to favour the onset of the disease such as cinchophen and its derivatives. It is to be remembered in this connection that it may be impossible to ascertain the true history, either because the patient is unable from the severity of the illness to give information, or unwilling, as for example in the case of a pregnant woman who has been taking abortifacients. A careful case history may however give some clue to the nature of the illness, though not in the idiopathic cases. Of more importance is the nature of the onset of the illness and its course. Individual cases vary, but the sudden onset of unexplained vomiting and jaundice in a previously healthy person, followed by the rapid development of severe nervous symptoms, especially if occurring in the course of pregnancy/

pregnancy is very suggestive. On the other hand two stages of the disease may be observed, jaundice with indefinite gastro-intestinal symptoms and malaise, followed at a variable interval by a sudden exacerbation of symptoms, with added nervous complications. Intermediate forms may occur between these two extremes.

JAUNDICE - is a fairly constant feature, though it may be absent even in the severest cases. Usually however, it is an early and significant symptom. Its significance is increased by the absence of the causative signs and symptoms of other forms of jaundice, by the association of vomiting and nervous manifestations, and the absence of pyrexia.

NERVOUS SYSTEM MANIFESTATIONS - Of these restlessness, headache, apathy and drowsiness, progressing to semi-consciousness and coma, are the important features. Occurring along with jaundice and vomiting their importance cannot be over-emphasised. Stander (44) believes they may be of significance as prodromal symptoms in pregnancy and points out that persistent vomiting, dizziness and headache occurring near term in a gravid woman must be regarded as signs of impending hepatic destruction.

VOMITING - is a constant feature of these cases. Sudden in onset, and though at first it may be intermittent/

intermittent in the gradual onset type of case, it is sooner or later recurrent, and becomes repeated and persistent. It may be, and frequently is associated with blood, which may be present as frank blood or more usually as altered blood. The almost black vomitus of the later stages is a striking feature, and is often present even when the patient is deeply comatose. (Vide Case 2. and Standers Case (44))

LIVER DULLNESS. - Diminution of liver dullness is the most important clinical feature of the disease, and its demonstration in a case of jaundice, persistent vomiting and drowsiness may be regarded as pathognomonic. Care is essential however in demonstrating this sign and the fallacy due to diminution of the liver dullness from the presence of gas or fluid exudation in the peritoneal cavity, as for example in a perforated peptic ulcer, must be borne in mind.

THE URINE. Opinions differ as to the importance and presence of certain changes in the urine in acute yellow atrophy, but there is agreement on the following. (8)
(18) (9)

Amount. - usually diminished, especially towards the end.

Colour - usually high coloured from the presence of bile pigments. The degree of colour is largely dependent on the degree of jaundice present, and since cases do/

do occur where jaundice is absent, bile pigment is absent in these cases, and hence the only alteration in colour is due to concentration.

Protein - as albumen, is generally present, and casts may also be present.

Sugar - invariably absent.

Nitrogen Excretion - the total nitrogen excretion may be diminished, normal or increased. Of this the urea nitrogen is lowered and the ammonia nitrogen is increased, and maybe increased from the normal 5 per cent up to 20 per cent according to Kollleston (8).

Uric Acid - may be normal but is commonly increased in amount.

Other points in the examination of the urine are the presence of leucine and tyrosine, and the presence of acetone bodies. There do not appear to be a constant finding and cases occur in which the former are absent (44) (45) and furthermore leucine and tyrosine have been reported in the urine in other diseases.(8)

THE BLOOD CHEMISTRY - in jaundiced cases bile pigment is present in excess, and the icteric index is raised, but the Van den Bergh reaction gives no information of diagnostic value and often gives a biphasic response according to Stander and Cadden (44). There is general agreement that the amino-acids in the blood are increased, as also in the amount of uric acid.

The/

The non-protein nitrogen is generally increased, but variable amounts of both the non-protein nitrogen and urea nitrogen are found. Standen and Cadden's case showed a decreased urea nitrogen (44) whilst Duncan and MacLachlan's case showed an increase (45). In Howard's cases (9) the figure was variable, increased in one, normal in another, and decreased in a third case. The blood sugar is usually decreased (8) (44) though in Duncan's and MacLachlan's case (45) which recovered, the figure was normal. The CO₂ combining power appears to be low.

The finding of increased amino-acids, increased uric acid and bile pigment are confirmatory evidence of hepatic damage.

DIFFERENTIAL DIAGNOSIS. The following conditions need to be considered in arriving at a diagnosis.

1. Phosphorus Poisoning. This rarely presents difficulty as the history, the predominance of gastric symptoms and the relatively slight nervous symptoms give a clue to the true diagnosis. Further in phosphorus poisoning there may be a period of comparative health between the first and second stages of the disease. Finally a progressively diminishing liver dullness and a falling urine urea are strongly in favour of acute yellow atrophy.

2. Other varieties of jaundice - especially acute infective jaundice and the so-called "icterus gravis". This may be very difficult and even impossible, since an infective jaundice may develop into an acute yellow atrophy. Since the two conditions overlap, the case is likely to be regarded as an infective jaundice if recovery follows. If on the other hand there is a fatal termination, the original diagnosis of acute yellow atrophy (if such has been made) is adhered to. The chief diagnostic point when acute yellow atrophy is not present, is the absence of liver shrinkage or the detection of an enlarged liver, which is the usual finding in cases of icterus gravis.

3. Delayed Chloroform Poisoning - What has been said of infective jaundice applies equally well to delayed chloroform poisoning, and distinction between the two conditions may be impossible since the one may become the other. The history is of no great help, since the fact that chloroform has been administered is no justification for the assumption that the disease is delayed chloroform poisoning. The only distinction that can justifiably be made is based on the size of the liver; if a diminished liver or better still a progressively diminishing liver can be demonstrated it is reasonable to make a diagnosis of acute yellow atrophy; if on the other hand there is no decrease in size/

size of the liver, a diagnosis of acute yellow atrophy may be regarded with suspicion.

4. The Toxaemias of Pregnancy - The question of differentiating acute yellow atrophy and the toxaemias of pregnancy only arises if jaundice supervenes in such a case. The symptoms, urine analysis, clinical course, blood pressure and absence of jaundice obviously preclude confusion in most cases. But if jaundice does arise in a case of pregnancy toxaemia the differentiation may be impossible, for the remarkable similarity between the end stages of some cases of eclampsia, and acute yellow atrophy has already been pointed out (vide supra - Etiology). It would appear that eclampsia and the toxic vomiting of pregnancy, may terminate in acute yellow atrophy. But until we know more of the nature of the toxaemias of pregnancy we cannot reach any definite conclusions as to differentiating the two diseases. The possibility of the development of acute yellow atrophy in the toxic vomiting of pregnancy must always be remembered.

COMMENT.

In applying these facts to the two cases presented there can be little doubt as to the correctness of the diagnosis in Case 1. All the classical signs and symptoms are typified...sudden onset of persistent vomiting/

vomiting, blood in the vomitus, marked jaundice, severe nervous symptoms, bilious urine, and diminished liver dullness. The last named sign, the diminished liver dullness, being of particular importance since the significance of this point has been established as the one sign justifying a distinction from delayed chloroform poisoning. The only possible dubiety is created by the fact that the patient recovered, and since recovery is so rare in this disease, its occurrence immediately throws doubt upon the correctness of the diagnosis. But undoubted cases of acute yellow atrophy which recovered have been recorded before, and again the existence of decreased liver dullness is pointed out, and moreover the sign was definitely present for five days it is to be noted. As the point is so important, I would also add that its presence was verified. Now it is quite conceivable that I might, in a fit of diagnostic enthusiasm, have erred in my clinical examination; but it is quite inconceivable that three other competent physicians, two of whom were consultants, examining independently and on different days, could have made the same error. Therefore I think it may be assumed to be correct and the diagnosis is established.

With regard to Case 2, the position is different for no diminution of liver dullness was detected in life and at the post mortem the liver was not found to/

to be diminished in size. In the absence of this vital physical sign there is a reasonable doubt as to the diagnosis. True, the other features were present; "black" vomiting, jaundice, deep coma, with sudden onset and rapid progression. But these signs and symptoms would fit equally well the diagnosis of delayed chloroform poisoning. It is greatly regretted that no report of the microscopic appearances of the liver is available, as this might have solved the problem, although as it has been stated, the two conditions are sometimes identical. That a doubt as to the diagnosis was also in the mind of the pathologist who conducted the post mortem is evidenced by the fact that he stated the cause of death as being necrosis of the liver, without mention of either acute yellow atrophy or delayed chloroform poisoning. The absence of bile from the urine when the patient was deeply jaundiced is remarkable, and I can offer no explanation for this. A diagnosis of acute yellow atrophy was not made during life, and quite frankly at the time I had no idea what the diagnosis was. I might also add that I am still uncertain as to how this case should be classified, as a case of acute yellow atrophy or as a case of delayed chloroform poisoning, but I have included it in this series because it illustrates so well the difficulty of distinguishing such cases.

certainly on the second day of the illness it decreased considerably only to return more deeply on the third day. It decreased steadily after the patient recovered full consciousness, but it was some weeks before it completely disappeared. The degree of jaundice is no indication of the severity of the illness and in very severe cases it is sometimes absent. The variability of the jaundice in yellow fever, has been explained by Klotz and Simpson (47) on the basis of the modern theory of bile formation by the reticulo endothelial system. They suggest that if the toxin is potent enough to arrest the function of the Kupffer and other pigment forming cells, no bile is formed and therefore no jaundice occurs. This applies equally well to acute yellow atrophy and where jaundice occurs we may assume that the causal agent whilst able to kill liver cells is not potent enough to prevent the reticulo-endothelial cells from functioning. This agrees with the findings at necropsy.

4. Pallor. This was a marked feature of the severest stages of the illness in Case 1. That jaundice tends to mask the pallor may account for the fact that no note of this observation has been found in records of other cases.

B. Gastro-intestinal symptoms.

1. Nausea. This is a common early symptom of the disease. It is not of course peculiar to acute yellow/

yellow atrophy, but its unexplained presence, especially if persisting in circumstances where hepatic damage is likely to occur, should be regarded with suspicion. The nausea may be accompanied by retching as in Case 1.

2. Vomiting ... has already been described (vide diagnosis). It was present in both these cases, as was blood in the vomitus. Haematemesis is due to congestion in the blood vessels of the stomach and lower end of the oesophagus, from portal stasis.

C. Nervous Symptoms.

1. Restlessness... was an early symptom in both the cases described; it has been noted in the early stages by other observers (46). It is regarded as a cerebral symptom, the result of central nervous system irritation and more commonly occurs later in the course of the illness, with the onset of the severer nervous system manifestations.

2. Apathy and Drowsiness, along with restlessness are early signs of nervous system involvement. They merge gradually or rapidly into stupor and ultimately coma. They are present in all cases.

3. Coma... present in both these cases and is a very constant characteristic of the disease. The depth of coma is an indication of the severity of the illness, since like the other nervous symptoms it is believed to be due to the effect on the central nervous system/

system of hepatic failure. Therefore the greater the hepatic damage the more severe the effect on the nervous system and the deeper the coma.

4. Twitching of muscles. This was observed in Case 1 but was not a marked feature. It is of serious significance as a warning sign of impending convulsions.

5. Dilatation of the pupils. This is frequently observed in the comatose stage of the illness and although it frequently occurs in other diseases, it serves to differentiate the coma of acute yellow atrophy from that of morphine and uraemia. Its presence was noticed in Case 1.

6. Stertorous breathing .. was noted in Case 1. It is a sign of deepening coma.

OTHER SYMPTOMS which have been recorded in acute yellow atrophy, but were not present in these cases are:-

1. Abdominal pain.. in the liver region. Apparently a common early symptom. (8) (46) (44). It may be associated with tenderness. (48) (9) (45).

2. Anorexia and wasting have been noted in Howard's cases (9) but these cases were of the subacute variety. The disease in pregnancy is usually too rapid in its progression for either of these symptoms to be noticeable.

3. Constipation is the usual finding (49) (8) but/

but diarrhoea has been found (9). In this series, treatment and the rapidity of the disease, prevented the appreciation of these symptoms.

4. Oedema of the feet has been noted in at least one case. (46).

5. Haemorrhage. Apart from haematemesis, haematuria, bleeding from the nose and into the skin and conjunctiva have been recorded. (8) (9) (49).

6. Persistent Headache which is often very severe (46) (49). This may be an early symptom or may precede the onset of the graver nervous symptoms when it may be accompanied by photophobia (8).

7. Muscular rigidity preceded coma in two of Howard's cases (9).

8. Dizziness was a prodromal symptom in Stander's case (44).

9. Delirium amounting to mania occasionally occurs. (9) (50).

10. Convulsions are mentioned by Rolleston (8) who states that they may be a terminal feature of the disease. It does not appear to be a frequent symptom for I have only found one case reported in which convulsions occurred (9).

CLINICAL COURSE.

Rolleston (8) divides the course of the disease into two stages; the first lasting five to six days/

days but sometimes extending to weeks, with malaise, gastro-intestinal disturbances and jaundice; the second rarely lasting more than a week and characterised by nervous phenomena and the "typhoid state", culminating in coma and death. Since the cases presented in this paper were both associated with pregnancy in which the course is somewhat modified it is proposed to confine the discussion of the clinical course to these cases.

In pregnancy, and especially in the puerperium, Rolleston's two stages are rarely so clearly and often not at all defined, the disease running a much more severe and acute course, and usually terminating fatally within a week, often in a much shorter time. All the fatal cases cited in this paper have died within six days of the onset of the disease, one case died within one and a half hours (51) and the average length of survival after the first onset of symptoms appears to be three to five days. Case 1 of this series lasted six days in its acute stage though convalescence was prolonged for some weeks after this, whilst Case 2 died within twenty-four hours of the first symptom. In Case 1 however two stages were discernible, and between the two stages there was a brief period of some twelve hours when improvement was noticed. The onset was heralded by restlessness and nausea, quickly followed by/

by vomiting, jaundice, apathy and weakness, which lasted twenty-four hours. Then came the temporary improvement with cessation of the vomiting followed again by apathy, drowsiness and coma, but fortunately the vomiting did not recur. This temporary improvement is difficult to understand, but it is believed to have been due in part to the giving of intravenous glucose. This it is presumed gave a functional stimulus to the liver tissue which remained healthy, and to those liver cells which were only partially damaged, but still survived and were capable of functioning, though possibly only partially efficient. This it is suggested produced a relative increase in hepatic output, only to be followed by recurrent hepatic insufficiency as more of the partially damaged liver cells finally succumbed to the effects of the original injury and ceased to function.

On the other hand is it not possible that the first period of severe illness, vomiting, apathy and jaundice was due to hepatic insufficiency, the result of the direct effect of the toxin (or whatever is the necrotising agent) on the liver? whereas the second period of illness, with the severe nervous symptoms was due not only to hepatic failure, but also to the effects of the absorbed autolysed products of necrosed liver cells? This would explain the delay in the onset of the/

the second stage, and the short period of improvement, since it must take some little time for autolysis of the liver cells to take place. Assuming this theory to be correct, death may occur either from hepatic insufficiency and would tend to occur early... or from an autointoxication, which would take a few days to develop fully. (Or from a combination of these two). This would explain the fact that some cases die very quickly, within a few hours, as one would expect if the liver has been severely damaged and almost ceased to function, whereas others which survive the lesser degrees of hepatic destruction, die in a few days from poisoning. No evidence can be produced in support of this theory, but experimental proof is possible, for if it could be shown that the nervous symptoms of acute yellow atrophy were produced in animals by the injection of the products of autolysed liver alone (or even after the animals had sustained slight liver damage say from chloroform) this would be strong evidence in favour of the theory. Until such evidence is forthcoming we can only accept the current belief that the nervous symptoms and the death of the patient are due entirely to hepatic insufficiency. On the foregoing theory the patient in Case 2 died from the immediate destruction of liver cells and consequent functional failure of the liver.

To/

To return to more practical considerations and the second stage of the illness of Case 1. The drowsiness and apathy progressed into coma until the second critical period was reached on the evening of the fourth day of the illness, when the patient was deeply comatose, breathing tended to be stertorous and the pulse was fast and feeble. However symptoms regressed, slowly for twenty-four hours, then rapidly and within a few days the patient was normal save for the weakness consequent upon any serious illness. There were thus two critical periods in the patient's illness, the night of the first day, and the evening of the fourth day of illness.

The Pulse... in Case 1 varied considerably throughout the illness, but was always accelerated, ranging from 110 to 156 per minute. It was found a reliable index to the patient's condition, being maximum in rate and of poor volume at the most critical periods, and on the first night was frequently irregular and uncountable. The hourly pulse chart which was kept during part of the illness, and is appended gives some idea of its variation. This finding is in agreement with most case records and has been emphasised by several writers (44) (46). Tachycardia was also observed in Case 2.

Temperature. Pyrexia is not a feature of acute yellow atrophy, the temperature remaining low until late in the disease. A rapid rise often to high levels of 105° and/

and 106° , commonly marks the last few hours of life. (8) (46) (44). These cases were no exception, and in Case 1 the maximum range was from 97.6° to 100° , the latter only being recorded twice. It bears no relation to the severity of the illness except possibly as a terminal sign. This would seem to be evidence against an infective origin of the disease.

Respiration... most case records note an acceleration of respiration as the disease progresses (8), this was not found in these cases, the respiratory rate never being more than 26 per minute in Case 1.

Reflexes. No constant finding is characteristic. In Case 1 the reflexes were exaggerated in the early stages. Some writers have noted a diminution or absence of reflexes (44) and a positive Babinski although syphilis may have complicated this case (9). These disturbances of the reflexes depend obviously on the degree of involvement of the nervous system, and may also be influenced by haemorrhages into the meninges.

Blood Pressure... this remains unaltered or may become lower as the disease progresses (46). A raised blood pressure was present in Case 1 as in Standen's case (44) but in both these cases pre-eclamptic toxæmia complicated the picture. It is to be noted that in the case reported here the blood pressure fell steadily throughout the illness, just in the way that is usually/

usually found in recovering cases of pre-eclamptic toxaemia.

Liver Dullness.... little need be added about this sign though its importance cannot be over emphasised. It is diminished throughout the illness in Case 1 but returned to normal as the patient recovered. This has been noted in other cases (49). The degree of diminution of dullness may be regarded as an indication of the severity of the disease, since in most fatal cases the dullness disappears entirely (44) (8).

Splenic enlargement has been noted in some instances (9). It was not detected in either of these cases.

The Urine... has already been described fully under diagnosis. It is interesting to note however that in Case 1 where albumen was present in considerable amount from pre-eclamptic toxaemia before the onset of the liver complication, the amount of albuminuria decreased steadily throughout the illness. Further the total amount of urine passed, which had been small, increased rapidly when large amounts of fluid were given. The bile in the urine varied in amount from day to day and persisted for some time after the patient recovered.

The stool... The motions showed a variable amount of bile pigment, were pale throughout and for some days after/

after recovery but only clay coloured on one occasion towards the end of the illness. This is the usual finding and is not surprising in a disease in which the jaundice although of the toxic variety, may be partially obstructive from the anatomical disturbances occurring in the liver.

COMMENT.

From these comparisons it is seen that the two cases presented well illustrate the main signs and symptoms of acute yellow atrophy of the liver. The earlier history of Case 1 also gives a remarkably typical picture of gradually progressing pre-eclamptic toxæmia, commencing about mid term with a marked increase in weight. The significance of this was not appreciated at the time, but McIlroy (52) points out that undue increase in weight is often the earliest sign of pregnancy toxæmia. This was followed by a succession of signs and symptoms, cramps, a rising pulse rate, a gradually rising blood pressure, headache and vomiting, and occurrence of oedema and the appearance of albumen in the urine. The latter increasing in amount, with a still rising blood pressure and a falling urinary output, in spite of treatment, until interference was imperative. The disappearance of these symptoms and signs after labour, in spite of the onset of/

of acute yellow atrophy is no less striking, and offers hope and encouragement in what may appear the most hopeless of illnesses.

Mental confusion was a disturbing sequelae for some twenty-four hours following recovery in Case 1, but this soon disappeared and was presumably a result of toxæmia and disorientation from the loss of several days consciousness. Rolleston (8) notes a case of his in which mental derangement occurred for several months but which eventually recovered completely. No satisfactory explanation has been found for the mild relapse which occurred during convalescence in Case 1. No cause was found at the time, and there were no symptoms suggestive of the liver being at the root of the trouble, but it has been assumed that a little overactivity, with possibly also a too sudden increase in diet temporarily upset a still sensitive metabolism which was slowly adjusting itself to normality.

PROGNOSIS.

In a disease so serious and so fatal the prognosis must always be of the gravest, though as Case 1 clearly shows it need not be entirely without hope. Other cases of recovery have also been reported though rarely, Duncan and MacLachlan's case recovered (45), Grant and Miller (49) recorded two cases which recovered although in one case the diagnosis is not definitely established as acute yellow atrophy; a case of recovery is cited by Eden (53) and Wickam Legg collected 28 cases of reputed recovery (54). It must be emphasised however that once the disease is established, the outlook is extremely grave and Rolleston (8) states that if recovery does take place the disease must have been of the subacute variety.

In a disease in which recovery is so rare, the prognostic significance of signs and symptoms is necessarily obscure, but there are certain factors which seem to influence the outcome. Thus cases occurring in pregnancy are peculiarly fatal and as we have noted their course is rapid and severe. The condition of the kidneys has also been stated by Rolleston to be of importance, the presence of lowered renal function favouring a fatal issue. Whilst his contention is accepted as true, the recovery of Case 1 and the gradual decrease in signs of renal impairment throughout the illness/

illness, show that such renal impairment does not necessarily preclude recovery. The persistence of vomiting, and the severity of the nervous symptoms are of serious prognostic omen, but it is believed that in cases where the vomiting can be controlled or where it stops spontaneously as in Case 1, the chances of survival are improved.

The blood chemistry gives some indication of the severity of the disease, the higher the uric acid and amino acid values the more severe the degree of liver damage. It is also suggested that in cases with a normal or only slightly lowered blood sugar level in the early stages, recovery is more likely than if the blood sugar is low. The evidence adduced for this is the fact that in the cases in which blood sugar estimations have been obtained, with one exception the cases which recovered had a much higher level of blood sugar than those which died. It is regretted that no blood sugar estimations are available from Case 1.

Treatment is naturally of importance in the prognosis, and it is believed that the prompt and vigorous institution of appropriate treatment (*vide infra*) greatly favours the chances of recovery. Early treatment is especially important. A progressive and rapidly diminishing liver dullness in spite of treatment is a most unfavourable sign. Other symptoms of prognostic/

prognostic significance have been indicated under
symptomatology.

With regard to the duration of the disease. In
pregnancy or the puerperium we have noted that the ill-
ness runs its course in less than a week, sometimes
within a few hours. In other cases of the acute type
a fortnight is the usual limit, though survival for
longer periods has been recorded. (9).

TREATMENT.

In the absence of precise knowledge as to the cause of acute yellow atrophy there can be no specific treatment, but certain principles of treatment may be laid down. The first is prophylaxis, a council of perfection applicable to all diseases, but of especial importance in this disease where as it has been shown, certain predisposing factors are well recognised. The second is the early commencement of treatment and the courageous perseverance with treatment, for it is clear from the rapid development and course of the illness in some cases (vide supra) that hepatic damage may occur in a very short time, and the greater the speed with which measures are instituted to limit and control the damage and its effects, the less damage and the less the effects likely to accrue. The two cases described drive home the force of this contention although it is realised that Case 1 was probably not so severe as Case 2. In Case 1, treatment was commenced as early as possible, in point of fact intravenous destrose was given (quite fortuitously) in small amount before the diagnosis was made, indeed before the onset of the first recognised symptom, and the patient recovered. Furthermore treatment in this case was vigorously pursued throughout although a fatal outcome appeared inevitable, and the patient appeared to be going/

going downhill in spite of the treatment. On the other hand in Case 2 where the nature of the illness was not recognised and the importance of treatment was not appreciated, effective treatment was not begun until severe symptoms had been present for some eighteen hours and death was the result. (Chronologically Case 1 preceded Case 2 by a year). What would have been the outcome if treatment had been given promptly, and especially if glucose and fluids had been given freely during labour as they should have been, it is impossible to know, but it is believed that the patient's life could have been saved. The third principle is that once the disease has been recognised, treatment must be directed towards relieving the work of the liver, encouraging the best possible conditions for liver cell recovery to take place, and sustaining the general condition of the patient until such time as the liver does recover. The following are the methods available to this end.

A. Prophylaxis.

1. The avoidance of potentially toxic substances such as phosphorus trinitrotoluene and trichlorethane.
2. More care in the employment of such drugs as cinchophen and its derivatives in therapeutics and extreme caution in the use of arsenical compounds in the treatment of syphilis. Howard (9) recommends the giving/

giving of 0.6 grams of sodium thiosulphate in 20 cc. of distilled water intravenously once daily for four days if toxic symptoms develop after arsphenamine.

3. Discrimination in the use of chloroform. The widespread employment of this anaesthetic in midwifery, and the erroneous belief that a pregnant woman is not susceptible to the harmful effects of chloroform is considered an important factor in the incidence of acute yellow atrophy. It is a striking fact that from a series of 26 deaths from acute yellow atrophy in pregnancy, 12 had received chloroform. (51). It is believed that especially great care should be observed in the employment of chloroform in pregnancy. Its use is contraindicated also in the presence of severe bacterial infection, in pre-existing liver disease or where starvation or vomiting has been present. Furthermore it is believed that its use in the treatment of eclampsia is attended by grave risks of hepatic complications and that further inquiry into this point is urgently needed. In this connection it is realised that the rarity of acute yellow atrophy may justify the risk of chloroform when other indications necessitate its use, but the risk of degrees of hepatic damage less than acute yellow atrophy must be remembered. Therefore it is suggested that in all cases where chloroform is used for anaesthesia, routine pre-medication with intravenous glucose is indicated.

What is
Shogmoff's
univocal
results?

4. The avoidance or adequate treatment of factors favouring the occurrence of hepatic damage, especially starvation, persistent vomiting and insomnia; and the encouragement of an adequately balanced diet.

5. The early recognition of symptoms which may precede the onset of acute yellow atrophy, especially unexplained headache, dizziness, nausea or vomiting in late pregnancy.

B. Treatment of the established disease.

The methods employed in Case 1 will be discussed first, followed by the other procedures which have been adopted.

1. Rest in bed in the prone position. This is important since it is desirable that the nearest approach to basal metabolic conditions be attained so that the demands made on the liver may be minimal. There was no difficulty in obtaining this in the case described, the only accessory measure employed being the giving of paraldehyde per rectum on one occasion. It is suggested that this drug in maximal doses is the method of choice in controlling restlessness and delirium since it has no toxic effect on the liver. Chloral hydrate is contraindicated in this disease on account of its toxic action on the liver and kidneys (55). Where paraldehyde is ineffective morphine should be given (8) (44). Bromides in full doses may be of value (8).

2. General Nursing. Efficient nursing attention is as important in the treatment of this disease as it is in the treatment of pneumonia. It should be designed to relieve the patient of all effort, and nursing cooperation is essential if fluid is to be given in the necessary quantities. Particular attention to skin, bladder, bowel and oral hygiene should also be paid. It is suggested that cases of acute yellow atrophy should be "specialized" as it is believed that such a case requires ceaseless attention. In Case 1 we were fortunate in having the assistance of an extremely capable private nurse to whom I am sure we owe much of the successful result. For this and other reasons hospitalisation is desirable. As in most illnesses fresh air is helpful.

3. The Bowels. In this case the bowels were controlled by calomel and Epsom salts. Calomel in $\frac{1}{4}$ grain tablets was given every hour until 2 grains had been given and was then followed up by half an ounce of magnesium sulphate in a small amount of water. The effect was very satisfactory and is suggested as the method of choice. Enemas may also be employed if required...in Grant's case of recovery enemas only were employed every second day (49). Excessive purging is both undesirable and harmful, a regular and free action of the bowels once in the day being all that is required.

4. Control of Vomiting. This may be very difficult. In this case it ceased spontaneously after the giving of intravenous glucose. If sufficient fluid and glucose can be administered by intravenous and rectal routes the withholding of fluids by the mouth is likely to assist control of this troublesome symptom. Howard (9) and Rolleston (8) recommend Bismuth, cocaine or morphine. Small pieces of ice orally are a useful adjunct to treatment.

5. Fluids. Although there is general agreement that the provision of fluid is important in the treatment of acute yellow atrophy, it is believed that many cases require far greater quantities of fluid than is commonly supposed, and that a relative dehydration usually present in such cases militates against survival. Bingham (56) in a recent article on the water requirements of surgical patients showed that an unsuspected dehydration occurs under the existing post-operative regime, and that this may be severe. He showed that the minimal fluid intake in the days following operation should be five to seven pints, if necessary by an intravenous route, and points out that extra fluid must be added for any lost by vomiting. I suggest that a similar state occurs in acute yellow atrophy, and since vomiting is often severe and the amount of fluid intake being limited to that supplied intravenously/ .

intravenously along with glucose (usually 750 to 1000 cc. twice or three times in twenty-four hours) a serious water lack is present. Certainly in this case good results followed the giving of large quantities of fluid. Glucose fruit drinks and other bland fluids were given orally every half hour during the illness, both night and day, the average daily intake being 9 to 10 pints. If oral fluids are not tolerated or a sufficient amount cannot be given by mouth, intravenous or rectal saline with glucose should be given. The continuous drip method is of great use in the provision of fluid.

6. Glucose and other foods. The importance of supplying glucose is paramount and along with the provision of fluid is the most hopeful line of treatment. It has already been noted that in acute yellow atrophy the blood sugar is usually decreased, thus glucose may be regarded almost as a specific in liver disease. This has been recognised by Rolleston (8), Standen(44) and others, and the work of Titus (40) has confirmed the value of glucose in hepatic disease. In most of the cases of recovery cited, the administration of glucose has been the main feature of the treatment. In this case 50 cc. of 20 per cent dextrose was given intravenously on two occasions; once before the onset of symptoms of acute yellow atrophy in an attempt/

attempt to relieve nausea, and repeated after the diagnosis was made. Later at a six hour interval two intravenous infusions of a pint of 10 per cent glucose were given. After this fluids were well tolerated orally and large amounts of glucose were able to be given in this way. Standen(44) in his case gave 20% glucose intravenously at first intermittently later by the continuous drip method. Grant's case (49) received glucose rectally and orally. Titus (40) urges the use of full doses of glucose for the liver damage of eclampsia, 20 to 25% for intravenous use, and gives the therapeutic dose of glucose as 50--75 grams in 200 to 300 cc. of distilled water given intravenously taking at least an hour to administer it, and repeated four or five hourly as required.

With regard to insulin opinions differ. Titus believes it is contra-indicated, Grant and Miller used it in one of their successful cases giving 5 units twice a day. In this case 10 units was given after the first intravenous glucose but was not repeated as blood sugar estimations were not available. Its value is uncertain and if given its use should be controlled by blood sugar estimations. Glucose should thus be given by any or all routes, rectal, intravenous or oral so long as a sufficient amount is provided.

Other fluid nourishment is of subsidiary importance.

Milk/

Milk is advised by Rolleston and was given in this case. Its value as a food needs no emphasis but it is probably also of value as a source of calcium in a readily assimilable form. Abundant fruit juice is well tolerated, as orange or lemon juice and serves as a good vehicle for glucose and adjuvant for fluids. It also supplies vitamin C. Marmite was added to the milk in this case, with the object of supplying vitamin B which on theoretical grounds should assist recovery. It might also be given as the now available intramuscular preparation. There is no contra-indication to its use, and it may be of value and therefore should be given.

7. Anhaemin. 2 cc. was given intramuscularly in this case. I have found no other record of its use in this disease. Since it should assist liver function its use might well be encouraged in similar cases.

8. Alkalies. On the grounds of a tendency to acidosis in acute yellow atrophy, many workers believe that alkalies should be given. Orsler (12) suggests 2% sodium bicarbonate rectally and Rolleston (8) gives one drachm of Sodium bicarbonate three times a day orally or 3 drachms to the pint intravenously with 10 to 20% glucose. Standen (44) also makes use of this method and considers it should be given if the blood shows a decreasing alkali reserve. It was only given once/

once orally in this case, as at the time it was considered of doubtful value. Since studying the literature it is agreed that its use is rational, but it should be given with caution and controlled by blood and urine examination. The presence of acetone bodies in the urine is an indication for its use.

The following measures have also been adopted, but were not used in this case.

1. Calcium administration - administered orally or intravenously as calcium lactate or calcium gluconate. Eden's case (53) of recovery was treated with intravenous glucose and calcium. Minot and Cutler (57) have shown experimentally and clinically that calcium and glucose are interrelated, and that a low blood sugar in cases of liver disease can be raised rapidly to normal levels by calcium medication. This furnishes a basis for its use in acute yellow atrophy, since it may thus tend to stabilise metabolism and assist the liver. Calcium was given in full doses in this case until the induction of labour, and it may be assumed that a sufficient supply had been stored in the body. It should certainly be used as an aid to treatment.

2. Blood Transfusion was given three times in Duncan and Maclachlan's case of recovery. (45). It was used along with venesection in Hsiung's case (46) but/

but was unavailing. No rational basis for its employment has been noted, and its use must be regarded as experimental.

3. Horse Serum was given by Rolleston (8) in one case which eventually recovered. No other note of its use has been found. It is interesting to note in conjunction with the earlier discussion on autolysis that horse serum has anti-autolytic properties. Further evidence would be of great interest in this connection.

4. Intestinal Antiseptics such as salol and beta-naphthol have been suggested. There is no evidence pointing to an intestinal toxaemia as an etiological factor in the disease so that the employment of such agents seems unjustifiable.

5. Caffein and Diuretin have been advised to stimulate the flow of urine. Intravenous infusions eliminate the necessity for their use.

6. Urotropin has also been suggested for the jaundice. The use of this or any other drug without strong evidence of its utility is strongly contraindicated in acute yellow atrophy.

COMMENT.

On the basis of this evidence the greatest hope of survival rests primarily on the early and frequent administration of glucose and abundant fluid. Rest, quiet, fresh air and good nursing form the background/

ground to the treatment. More adequate treatment is possible if the resources of a laboratory are available so that hospitalisation is desirable. As useful adjuncts in the diet milk and fruit juice play a part, and the maintenance of bowel action, and the giving of calcium, anhaemin and vitamin B are important subsidiary elements in the treatment. The giving of alkalies may also be considered in suitable cases. It is believed that with more general application of these lines of treatment an improvement in the results might be observed. After the acute stage, care is desirable in the extension of activities, and the diet should gradually return to normal, commencing with a high carbohydrate diet, next adding protein and lastly fat. The usual convalescent treatment may be followed in all other ways, with the use of iron as being the most suitable tonic for these cases.

4. Our knowledge of the aetiology of the disease has been surveyed but no definite aetiological factor common to all cases has been found.

5. It has been shown that in many cases, as in the ones presented, the aetiology is not a single factor but a combination of factors. The occurrence of unexplained idiopathic cases in which no known aetiological factor is discernible, is accepted.

SUMMARY AND CONCLUSIONS.

1. Two hitherto unpublished cases of acute yellow atrophy of the liver have been reported. Both occurred in the puerperium, one recovered and one died. These cases have been discussed from an etiological, clinical, diagnostic and therapeutic aspect comparing them with other reported cases.
2. The history of the disease has been briefly considered. Its rarity is confirmed and no evidence has been found to support the suggestion that there is a general increase in incidence.
3. It has been shown that acute yellow atrophy is not essentially a clinical entity, but a terminal condition which may arise under a variety of different circumstances.
4. Our knowledge of the etiology of the disease has been surveyed but no distinct etiological factor common to all cases was found.
5. It has been shown that in many cases, as in the new cases presented, the etiology is not a single factor but a combination of factors. The occurrence of unexplained idiopathic cases in which no known etiological factor is discernible, is accepted.

6. The toxic theory of the causation of the disease has been considered, and whilst being accepted as possibly correct, it has been shown that it is not necessarily so.
7. The suggestion has been made that the disease is more correctly appreciated if regarded as a metabolic disease and a fundamental disturbance of cell metabolism has been postulated as the basis of all cases. It has further been suggested that this disturbance of cell metabolism is probably in the nature of a disturbed carbohydrate metabolism and evidence has been discussed supporting this view.
8. The possibility of the existence of a hereditary predisposition, and of a hormonal factor in the etiology has been suggested.
9. The frequent association of the disease with pregnancy and the puerperium has been discussed and it is believed that this is due to the metabolic instability present in pregnancy. The prevalence of chloroform as a predisposing cause in pregnancy has also been noted, and is regarded as a frequent precipitating agent of acute liver necrosis, indistinguishable from acute yellow atrophy.

10. The pathology of the disease has been reviewed and discussed. It has been remarked that the outstanding pathological feature of the disease is necrosis of liver cells and the unsuitability of the nomenclature has been noted. The part played by autolysis in the pathogenesis of the disease has been observed.
11. The post mortem report of Case 2 has been compared with the usual pathological appearance. The only discrepancy noticed was the absence of liver shrinkage, which it appears may occur in acute yellow atrophy, though rarely.
12. The similarity of the liver changes in acute yellow atrophy and pregnancy toxaemia of all types has been pointed out, and the association of acute yellow atrophy and pre-eclamptic toxaemia in Case 1 stressed. It is agreed that the difference between the results of these conditions may not be so great as is generally supposed.
13. The diagnosis of acute yellow atrophy rests on the association of jaundice, vomiting, severe constitutional and nervous symptoms, with a diminished liver dullness. The blood chemistry and urine analysis may be of assistance in diagnosis.

14. The diagnosis of acute yellow atrophy in Case 1 has been justified, but in Case 2 it has been found impossible to establish a differentiation from delayed chloroform poisoning.
15. The symptomatology of the two cases has been found to agree with other recorded cases. It has been noted that the signs and symptoms of pre-eclamptic toxæmia disappeared in a normal manner in spite of the complication of acute yellow atrophy.
16. The pulse has been noted as a reliable guide to the condition of the patient, whilst the temperature gave no indication of the severity of the illness.
17. A theory has been propounded that death in acute yellow atrophy may occur either from hepatic insufficiency or from auto-intoxication. It has been further suggested that the severe nervous symptoms might also be due in part to auto-intoxication from the products of necrosed cells. A promising line of research has been suggested on these lines, since some therapeutic indication might become obvious if it was proved that the products of autolysed liver cells cause some of the clinical manifestations.
18. The/

18. The prognosis is always grave, but it is believed that prompt, vigorous and continued treatment may be effective, and that contrary to the accepted belief the prognosis is never hopeless.
19. It is agreed that the prognosis is worse in pregnancy. Ominous signs in the illness are a progressively decreasing liver in spite of treatment, and persistent vomiting.
20. In considering treatment, the importance of prophylaxis has been noted. In this connection, the importance of vomiting, starvation and chloroform especially if present together in pregnancy has been particularly emphasised. It has been suggested that chloroform should be used with greater care and especially in pregnancy should be preceded by routine administration of intravenous glucose. The use of chloroform in eclampsia is regarded as dangerous.
21. In treatment, glucose and abundant fluids are the essential elements. It has been pointed out that the provision of fluids is usually inadequate.
22. Other useful aids to treatment which should be employed are, calcium, anhaemin, and vitamin B. The provision of efficient nursing is essential to success.

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DIET CHART.

(From which the diet was chosen in the period before induction of labour.)

Foods allowed.

Milk... total amount not to exceed two pints a day.

Bread and milk with sugar ad lib.

Milk $\frac{2}{3}$ Soda $\frac{1}{3}$.

Bovril.

Marmite.

Weak Tea, with sugar.

Rice.

Jelly, milk or sweet.

Porridge.

Junket.

Baked apple.

Stewed prunes.

Cauliflower with white sauce.

Apples, oranges, grapefruit, grapes, bananas,
peaches, pears.

Stewed apples, oranges and banana salad.

Cream cracker and plain biscuits, limited amount.

Thin toast.

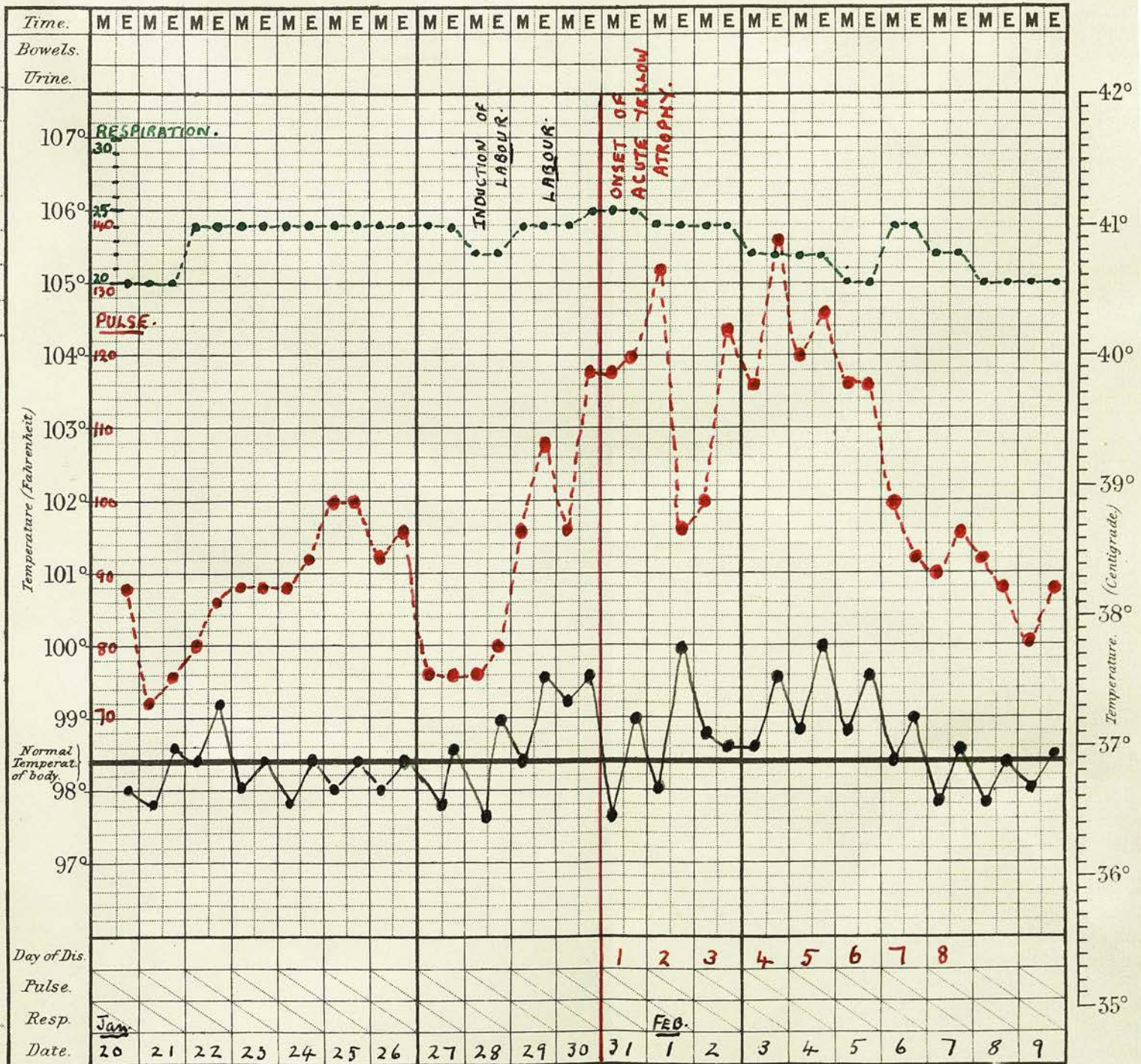
Butter.

CASE 1. Chart showing pulse Temperature and
Respiration.

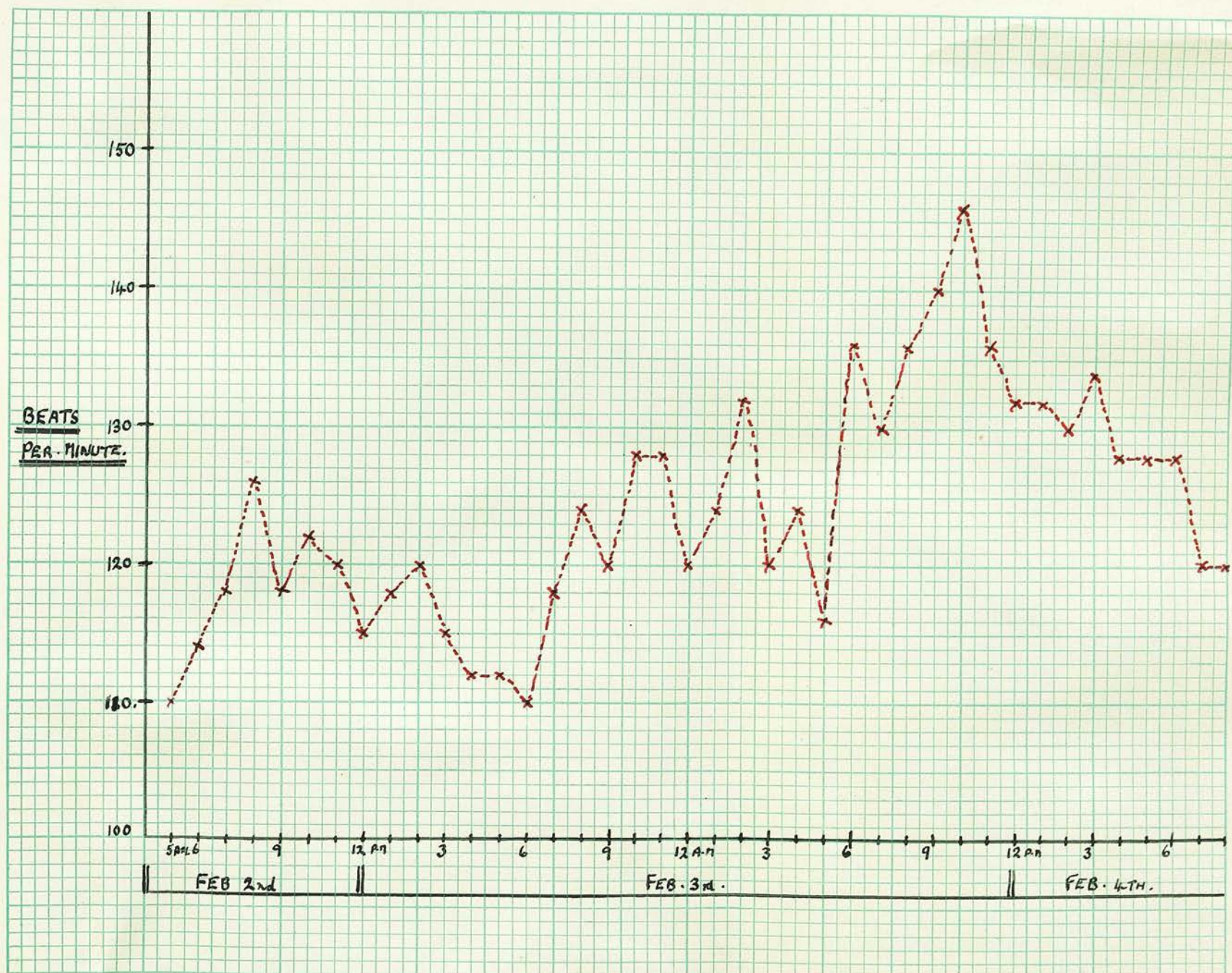
DISEASE.
ACUTE YELLOW.
ATROPHY
Notes of Case.

Name { MRS. A.
Age 32
Diet —
Case Book No. I.

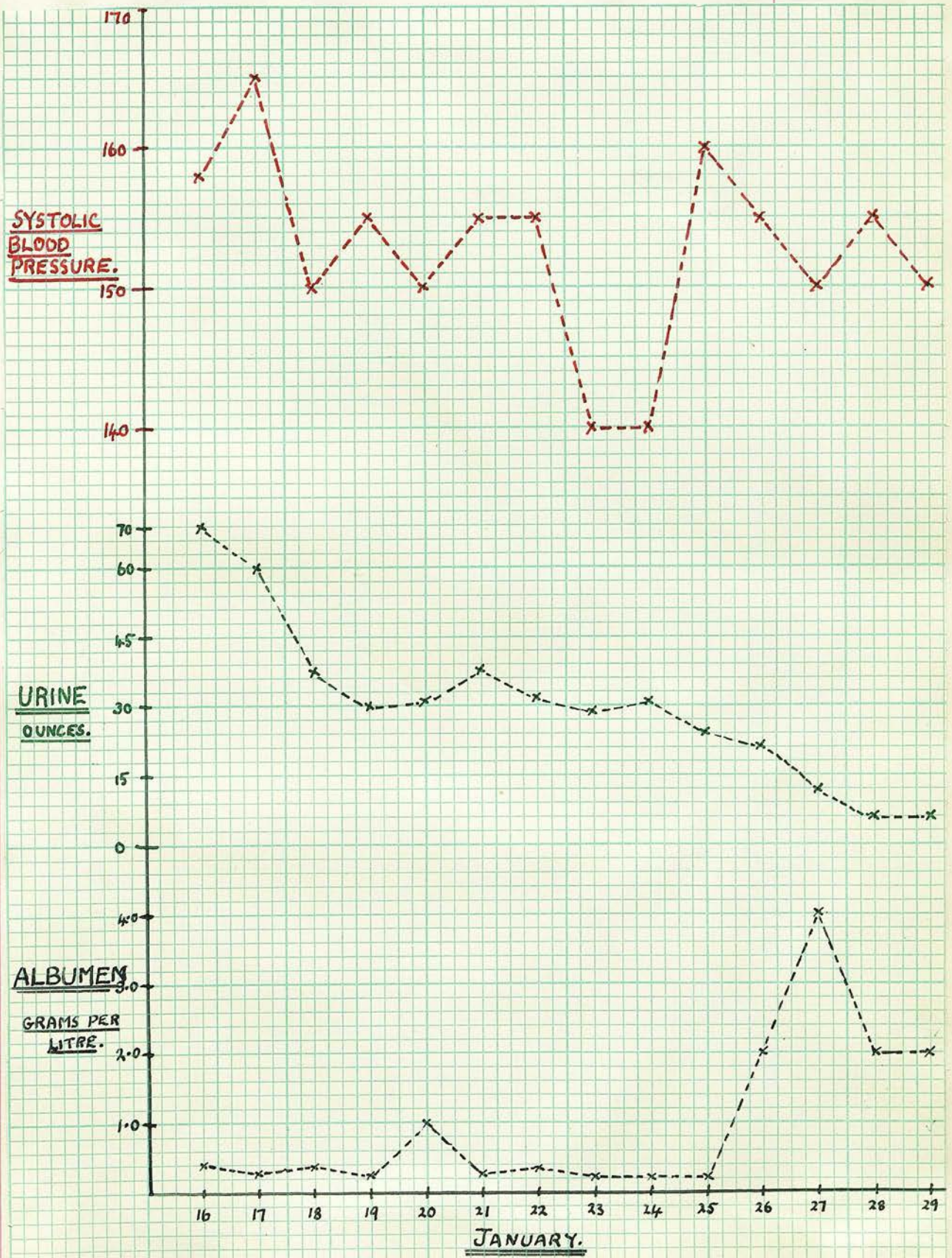
Date of admission.
Result



CASE 1. Chart of hourly pulse rate during severe
stage of acute yellow atrophy.



CASE 1. Chart showing the Blood Pressure, Albumen and Amount of Urine before labour.



increased requirements of labour, and especially in Case 2 where labour was prolonged and exhausting. In other words a state of physiological ^{IM}unbalance existed, in which catabolic processes would tend to predominate. Since cell life is the result of anabolic and catabolic balance - conditions were favourable to cell destruction. These conditions were even further exaggerated, markedly so in Case 1 by the occurrence of vomiting. In such a state it can be appreciated how a cell toxin was peculiarly liable to produce gross effects. It may be added that at the time when these cases occurred, the significance of these factors was not appreciated. It is only since I have studied these cases that I have realised the supreme importance of fluid and nourishment in such circumstances. Unhappily, death was the outcome in Case 2 and it is not possible to foretell whether the same result would have followed if fluid and nourishment had been provided by intravenous or rectal routes.

Another minor point suggests itself. The patient in Case 1 was herself a premature child, and her mother died of a hepatic disease (not acute yellow atrophy) which raises the question of heredity. No attention seems to have been paid to this point as I have found no reference to it in the literature. It is obvious that the disease itself is not familial, yet/

