A STUDY OF THE BIOCHEMICAL ALTERATIONS OCCURRING IN THE PRE-AGONAL AND AGONAL STATE.

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By

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CONTENTS

PREFACE

The work for this thesis was carried out in the wards of The Royal Infirmary, Glasgow, and later in the wards and laboratory of Robroyston Hospital.

The idea, which set me to work on the task of investigating the biochemical changes which might take place in the human body as death approached, was suggested by Dr. R.D. Campbell of Kirriemuir. He had occasionally noticed that certain constant changes occur in the pH of the urine of such patients.

When the idea had matured, the late Professor Noah Morris encouraged me to broaden the scope of the work to include certain electrolytes of the blood.

I am also much indebted to Dr. H.E.C. Wilson of the Royal Hospital for Sick Children for his interest in the work and interpretation of several of the biochemical findings.

I wish to express gratitude to Dr. David Smith of the Royal Infirmary, and Dr. M.A. Foulis of Robroyston Hospital, for placing their wards and laboratories at my disposal, and also to Professor Stanley Graham for helpful interest in this work.

INTRODUCTION

When the present study of the dying was commenced in early 1947, the problem was intriguing. So scanty was the literature that it was difficult to know how exactly to go about the task, or which electrolytes to study in order to demonstrate to best advantage any biochemical changes which might be happening in the dying patient.

It was not known at that time whether a constant pattern of changes, or any change at all for that matter, would be found. The work had to be built up brick by brick from a modest foundation, each discovery leading to another line of investigation, and each failure discarded.

The type of patient studied was selected. This was inevitable, because no change in the internal millieu could be expected in a man suddenly struck dead for example by a blow on the head, or in a patient dying suddenly of coronary thrombosis or cerebral haemorrhage. It was realised too that patients dying of chronic renal disease or diabetic coma would be unsuitable subjects for the present study

because of the known gross upset in blood and urinary biochemical constituents found in those conditions.

It was found that the changes taking place as death approached could but be demonstrated in subjects dying relatively slowly from such diseases as carcinoma, pulmonary and miliary tuberculosis, tuberculous meningitis, various types of cardiac failure, and the more slowly fatal intracranial disasters.

It was not long after the practical work commenced that unforseen difficulties connected with organisation and ethics arose. The aim was to carry out two or three estimations on the blood and urine during life, and a final estimation immediately after the death of the patient. Close co-operation was required from the nursing and resident medical staff, and this was fortunately forthcoming in most instances, but several cases were inevitably spoiled due to the fact that deaths were not reported promptly, or took place at inconvenient times. The advantages of "living in" were apparent, since deaths seemed to occur quite commonly during the early hours of the morning.

One had to be most careful in the manner of approach to a selected patient; the reason for withdrawal of blood had to be carefully concealed. Patients, particularly in a sanatorium, become very curious when they notice particular attention being paid by the same doctor to persons obviously

dying and recently dead. The situation became so delicate at times, that investigations on several patients had to be abandoned. This state of affairs could usually be avoided by judicious selection of subjects from a large number of wards, and maintaining a cloak of innocent secrecy regarding the purposes of venepuncture.

Cardiac puncture after death is not a strictly legal procedure in the absence of written permission of a relative, but in practically every case the operation was carried out expeditiously, leaving practically no sign of interference, and the legal aspects ignored.

The host of biochemical techniques which had to be learned and standardised to perfection seemed at first to be overwhelming, but as the investigations proceeded it was found that a definite laboratory technique was acquired which could be applied to almost all determinations, and so the task lost a lot of its original formidable proportions.

Apparatus and reagents in the immediate post-war years were difficult to come by, and several minor alterations in technique had to be made and alternative methods used, but on the whole excellent facilities were available in the hospital laboratories in which the author worked, thus smoothing out many difficulties.

CHAPTER I.

HISTORICAL SURVEY

Very little work has been done on the subject of biochemical changes occurring in the agonal or pre-agonal state, and then usually as a reference to one or two blood estimations carried out incidentally in the course of some other work. Sir Lauder Brunton (1901) in his book 'Lectures on the Action of Medicines' wrote: "Amongst general anaesthetics, the most universal is carbonic acid, and it is a merciful provision of nature that almost every individual as he passes out of this world, passes out in a condition of anaesthesia. As the strength fails and respiration becomes feebler and feebler, carbonic acid accumulates in the blood; the nerve centres become dulled; the man becomes anaesthetic, becomes insensible to pain and to external impressions, and finally slips away."

Peabody (1913), while investigating cases of pneumonia noted that there was a progressive fall in the

oxygen content of venous blood in those patients who ultimately died. He investigated 10 patients.

In 1917, Whitney published a paper entitled "Studies on Acidosis - the immediate cause of death". This paper was apparently the first to appear in which the subject matter was exclusively concerned with the changes occurring at death.

Whitney found that the majority of patients at the moment of death showed a very marked acidosis, and that the acidosis was of short but variable duration preceding death, usually from a few hours up to several days.

He recognised that death of the respiratory centre was the essential element in the death of the body as a whole, but did not think that certain abnormalities such as incompetent kidneys, circulatory failure or malignant disease could unaided furnish the toxin necessary to paralyse the respiratory centre. He postulated that the toxin causing final paralysis was due to a terminal infection for which the underlying chronic process had prepared a favourable soil.

Preterminal infection was regarded by Whitney as being the main cause of the acidosis, and in all his 40 cases except one, acidosis was accompanied by infection.

In demonstrating terminal acidosis, Whitney relied on the measurement of the carbon dioxide content of the blood withdrawn within 10 minutes of death by cardiac puncture; his

results will be discussed in a later section. He also estimated the non protein nitrogen in several fatal cases and found that there was an increase at the time of death, often very great. This, he thought, indicated a marked tissue destruction.

Dautrebande & Davies (1923) showed that there was an average increase of 9 vols. per cent. in the alkali reserve of 7 patients suffering from extensive pulmonary tuberculosis, but they do not mention how long before death the estimations were made.

Meakins & Davies (1925) describe a case in the pre-agonal state as an example of gaseous acidosis. The patient had a right sided hydrothorax and an emphysematous left lung with superimposed purulent bronchiolitis. She had been markedly cyanosed, and had been kept alive for seven days by the administration of stimulants and continuous oxygen. On the day before death, during oxygen administration, her arterial blood was 79% saturated with oxygen and contained 85.5 vols. per cent. carbon dioxide. On ceasing the administration of oxygen, the arterial oxygen saturation fell to 18%, the carbon dioxide content remaining the same - 85.3 vols. per cent.

There appeared in The Lancet of 1926, a letter from Dr. Arthur MacDonald of Washington, D.C., urging medical societies to encourage a systematic and scientific study of

the dying hour, especially as regards the physiology and psychology of death. He wrote: "It is a curious fact that as yet, there seems to have been no systematic and scientific study of human death. There have been more or less sporadic efforts to make such investigations in exceptional and interesting pathological cases. But the regular order, so to speak, of the average manner of death is not known."

Despite Dr. MacDonald's appeal the literature during the following 20 years contains no systematic study of death, although several more sporadic observations on isolated cases appeared. This is surprising, because a very stimulating paper by Koehler, Behnemann, Benell & Loevenhart (1925) appeared about the same time in the "American Journal of Physiology". The paper was entitled "The Cause of Death from Anoxaemia", and although the experiments were performed on animals, they seemed to have a direct bearing on the human problem.

Koehler and his co-workers, as a result of these experiments came to the conclusion that reduced oxidation directly stimulates, and also induces an acidotic type of metabolism. The acidotic type of metabolism induced interferes with oxygen fixation by the cell, and thus further stimulates.

This vicious circle of oxygen want and acidosis continues until oxygen is reduced to the point which can support no functional activity. Then, there is depression or paralysis. Finally, the energy liberation is reduced to

a point which does not even meet the small requirement of the internal needs of the cell, which is unable to maintain the status quo, and the irreversible change, which we call death, supervenes.

The experiments and detailed conclusions which these workers made will be discussed later in relation to the findings in the present series of cases.

Cameron & Carmichael (1926) made the observation that in dying patients hypocorticalism may be partly responsible for some of the metabolic changes. The enlargement of the adrenals which occurs in acute starvation had hitherto been considered an hypertrophy, but it had now been shown by Cameron & Carmichael to occur just prior to death, and was probably an hydropic degeneration. The authors however do not discuss the particular metabolic changes which occur in dying patients.

A very full symposium on the behaviour of the blood lactic acid in various physiological circumstances and diseases was published by Jervell (1928). In one section he records the result of his investigations of the blood lactic acid levels in 7 cases of pulmonary tuberculosis in the final stages. In one case he found the first estimation to be normal, but a subsequent one to show an increased level of lactic acid. The interval between the estimations nor the length of time before death is not stated. Jervell concluded that pulmonary

tuberculosis in a more advanced stage is accompanied by hyperlactacidaemia, and that anaemia and weakened action of the heart are contributory causes to this increase. Jervell also found a considerable preterminal increase of blood lactic acid in cardiac insufficiency.

Kirk (1946) recognises the state of agonal acidosis in his monograph "Acidosis". He considers that the pre-agonal state is due to accumulation of organic acids, mainly lactic acid, and that the acidosis is due partly to tissue anoxia and partly to a terminal infection.

Towards the end of 1948 when the experimental work of the present thesis was nearing completion there appeared in "The Lancet" a review of a book by Ib Fabricius Hansen called "Investigations on Agonal Acidosis". It seemed that this work would be a very important contribution to the scanty literature on the subject, so a copy was obtained from Copenhagen. It reached the author in January 1949.

Hansen's work is in fact the fullest and most important account of the subject which has yet appeared. His investigations were carried out between 1940 and 1944, and the results compiled by the autumn of 1945. Unfortunately he died six months later.

He set himself the task of investigating the frequency and character of agonal acidosis using recognised and reliable techniques. Cases of renal disease and diabetes mellitus were omitted because of the profound electrolyte changes known to occur in those conditions, and which would tend to interfere with the interpretation of results in the experiments under review.

Thirty-eight patients were studied, and electrolyte estimations were performed on the blood withdrawn shortly before or shortly after death. The following determinations were carried out: pH, carbon dioxide, chloride, urea, protein, haemoglobin, oxygen, creatine, guanidine, amino-acids, lactic acid, pyruvic acid, serum sulphate and phosphate, total acetone bodies, total base, and non protein nitrogen.

Hansen made no attempt to investigate the development of the preterminal changes by performing a series of blood determinations, and in all his cases except two only one sample of blood was withdrawn, either before or after death. In Case 13, three determinations were made, and in Case 36, two. This fact tends to diminish the interest of the results, but their importance remains when they are considered together and analysed.

Hansen concludes that a fall of blood pH is usually found in the agonal state, values below 7.00 often being recorded, and in some cases often being the direct cause of death. He found that the plasma bicarbonate concentration, in contrast to the pH, is reduced in only about a third of the cases.

The acidosis was found to be mostly of a mixed type, intermediate between the metabolic and respiratory forms and different from the ordinary forms of acidaemia.

The lactic acid content of the plasma was constantly increased at death, and very high values were often obtained. Urea, amino acid and creatinine nitrogen values were also found to be increased in most cases, but Hansen could not demonstrate any constant relationship between the azotaemia and acidosis.

Hansen confined himself to the study of the blood electrolytes only, and surprisingly ignored the chemical and pH changes in the urine.

As a result of his experiments, Hansen suggests several lines of therapy which may be advantageously employed in certain cases where the prolongation of life might allow time for some specific remedy to act.

The measures suggested by the author include the administration of coramine or similar drug in order to maintain

the irritability of the respiratory centre. He cites the case of a woman, in extremis from extensive bilateral pneumonia, who was kept alive by large doses of intravenous coramine, while sulphathiazole and anti-pneumococcus serum had time to act on the bacterial invaders.

Oxygen therapy was often of use in the preterminal state, but the addition of carbon dioxide was contra-indicated because of the often markedly increased carbon dioxide tension of the blood.

In patients with marked bicarbonate reduction, Hansen believes that treatment with a 1.3% sodium bicarbonate solution given intravenously is indicated. Patients who were severely exhausted frequently showed at least temporary improvement.

CHAPTER II.

THE AGONAL STATE FROM A CLINICAL POINT OF VIEW.

The experience of the present study confirmed the general opinion that it is extremely difficult to predict the precise or even approximate date of death from clinical criteria alone.

A young man, seemingly robust, can die of bronchial carcinoma in five weeks, whereas an emaciated old man with chronic phthisis can hold on to the threads of life for many months. Unexpected complications such as tuberculous laryngitis may hasten death by depriving a patient of necessary food and drink.

In the final 24 hours of life, the clinical appearance is remarkably similar in patients dying of different diseases.

He tends to lie still, and in slipping down the bed off the pillows, he reveals his general weakness and apathy.

Although some patients may answer questions, the usual response is a slow turn of the head towards the questioner, and a dry croak from the throat. The eyes tend to be sunken and the lids half closed, causing the cornea to become covered with particles of mucus. The tongue is dry, and sometimes a definite foetor can be detected, especially in those dying of a long drawn out chronic illness. He often becomes incontinent.

The behaviour of respiration is interesting. In those whose death is due to a pulmonary lesion, dyspnoea has usually been evident for several days, whereas it may not have been in extra-pulmonary lesions, but in all cases during the several hours before death, a constant sequence of events has been observed.

Respirations are increased to about 30 or 35 per minute; they are usually regular, but may be of Cheyne-Stokes type; the breathing is noisy, and bubbling râles may be heard in the thorax, or mucous rattling in the throat.

This regular, rapid respiration is followed gradually by a slow, and irregular type of breathing. There are sometimes very long intervals between each breath which is seen to be drawn with great difficulty. By now the patient has dropped into coma out of which he cannot be roused; the

blood has drained from the face, and the tips of the nose, ears and extremities become cold and slaty in colour.

This period lasts from 30 minutes up to two or three hours, and marks the final stage before death. The pulse can barely be felt at the wrist, and is usually fast, often becoming irregular.

Death is heralded in most cases by one last breath, which is often of a sighing nature; the heart usually stops simultaneously with respiration, but may carry on irregular contractions for a few minutes.

The temperature is found to fall to a subnormal level several hours before death in the majority of cases.

And so the end comes. Such dramatic clinical changes are surely accompanied by equally dramatic changes in cellular biochemistry, and it is the object of the present work to study such changes as they are reflected in the blood and urine, and try to correlate them with the clinical picture.

CHAPTER III.

THE CHOICE OF BIOCHEMICAL ESTIMATIONS

It has been mentioned previously that when the present work was commenced, it was not known what precise biochemical changes would be found. Hansen (1948), on the other hand, set out to study agonal acidosis per se since apparently his teacher, Kirk, had encouraged him to do so as a result of his own personal observations. Hansen had the advantage of knowing exactly what he was looking for, and planned the selection of his determinations accordingly.

In the present series, the pH of the urine was studied first, followed soon afterwards by estimation of the titratable acidity and ammonia content. In a personal communication Professor Noah Morris suggested that the following blood electrolytes should also be studied simultaneously: plasma bicarbonate, chloride, phosphorus and calcium.

When the technique of these methods had been mastered, they were then included in the series.

After several cases had been studied, it was noticed that the plasma which was separated from blood withdrawn at death was very constantly of a deep yellow colour. Therefore the estimation of plasma bilirubin was included.

At this time, the level of plasma proteins was thought to be worth studying, and since the gravimetric method of estimation was available in the laboratory, this was also added to the list.

After several cases had been completed, the biochemical findings were examined and seemed to suggest that a state of acidosis was developing as death approached.

An obvious step was to study the pH of the blood and it was with much regret that this was found to be impossible. A pH meter was not available in the hospital at the time, and several colorimetric methods were considered, one of them being tried, but because of their inaccuracy it was not thought worthwhile to pursue them further.

This was unfortunate, because for the strict classification of the type of acidosis, two of the three variables, blood pH, plasma bicarbonate, and carbon dioxide tension, are required, as pointed out by Peters & van Slyke (1931).

However, it was becoming clear that although previous workers had laid stress on agonal acidosis, other factors also

entered into the picture, and so it was considered sufficient to demonstrate the trend of acid-base balance in the present series by means of the pH, ammonia and titratable acidity of the urine and the plasma bicarbonate.

The possibility that oxygen lack played some part in the development of acidosis in dying patients was suggested by the work of Koehler and his colleagues (1925) referred to in the Historical Survey. Also, the character of the respirations in the pre-agonal state made it likely that there was a degree of anoxia present. It was therefore decided to include the oxygen saturation of venous blood in the list of estimations made. It would have been more accurate to use arterial blood, but this was found to be impracticable, and with certain precautions discussed later, the results using venous blood were found to be suitable for the purpose of the present investigation.

Extensive studies of microbiology and cell respiration and metabolism have been carried out by notable workers like Pasteur, Warburg, Meyerhof, Kempner, Krebs and Cori, and the application of the results of their experiments to the problem of human death has been attempted. This inspired the inclusion of blood lactic acid and plasma phosphorus in the author's series.

Pasteur (1879) discovered that many cells form lactic acid in the absence of oxygen, and the Warburg-Meyerhof theory postulates that every decrease in cell respiration brings about a direct increase in lactic acid.

With tissue anoxia, according to Meyerhof's equation, there is a breakdown of hexose phosphate during the anaerobic phase, with the formation of equivalent quantities of lactic and phosphoric acids.

Baldwin (1947) also emphasises the importance of phosphorylation in the carbohydrate breakdown, both in aerobic and anaerobic metabolism, and so the behaviour of the inorganic phosphorus of the blood of dying patients might, in conjunction with the blood lactate, throw some light on the metabolic processes at that stage.

Whitney had found a preterminal azotaemia in several of his cases, and it was considered that this finding might be more fully investigated, so the estimation of the blood urea was included in the present series.

Since the plasma chloride was being investigated, the estimation of the urinary chloride excretion was included for the sake of completeness. No previous workers seem to have considered chloride metabolism in the pre-agonal state, and Hansen estimated only the plasma chloride, finding it low

in most cases. He did not put forward any firm views to account for the low values obtained, and finally decided that they were probably the result of a pre-terminal pulmonary infection.

CHAPTER IV.

THE LABORATORY ROUTINE:
Collection of Blood and Urine Samples.

When such a large number of estimations had to be performed, it was necessary to work out a satisfactory laboratory routine, especially since several determinations had to be done immediately after withdrawal of blood, for example, the plasma bicarbonate and blood lactic acid.

A small, easily portable box designed for the purpose was used to hold test tubes, bottles and syringe, and could be taken to the bedside. (Figure 1).

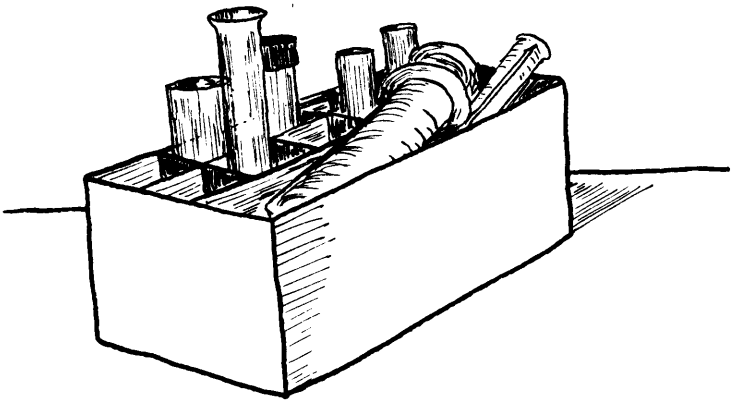


Figure 1.

A 20 cc. glass syringe with well fitting piston was used; it was sterilised and moistened with sterile liquid paraffin and fitted into one compartment of the box. Two sterile intravenous needles were carried in a test tube which fitted into the same compartment as the syringe. For cardiac puncture, a long, chest-aspirating needle was found to be most suitable, and this, although kept clean, was not sterilised.

During life, blood was collected from the median basilic vein, or other suitable vein in the antecubital fossa. For ten minutes previous to venepuncture, the patient kept the arms below the bedclothes and close to the body. This was important if the venous oxygen content was to be comparable between patient and patient and determination and determination, since Meakins & Davies (1920) showed that the relation between the oxygen saturation of arterial and venous blood may vary fifty-fold through the influence of external temperature. The lower the temperature, the less is the oxygen saturation of venous blood.

Air was completely excluded from the withdrawal system by expressing a small quantity of liquid paraffin from the syringe through the intravenous needle after it had been fitted.

The effect of venous stasis on the electrolyte content of a specimen of blood was demonstrated by Peters & his co-workers (1926). There is transfer of water from blood to tissues, concentration of proteins, and the plasma chloride diminishes, yielding its base to protein and carbonic acid. Venous stasis was therefore carefully avoided.

Twenty ccs. of blood were drawn into the syringe and immediately transferred to the following containers:-

a. About 7 to 8 ccs. of blood were delivered under paraffin to a 40 cc. screw-capped specimen bottle containing 20 mgms. of Wintrobe's oxalate mixture (12 mgms. Ammonium oxalate, 8 mgms. Potassium oxalate).

This blood was used for determining the oxygen unsaturation, haemoglobin content, lactic acid, and urea.

b. The remainder of the blood in the syringe was delivered to a 15 cc. pyrex, round bottom centrifuge tube containing liquid paraffin and 1 mgm. of heparin. (In several of the estimations, Wintrobe's oxalate was used.)

From this sample, the following determinations were made: plasma bicarbonate, bilirubin, phosphorus, chloride, and protein.

In several cases where the serum calcium was estimated, a separate tube was used in which 4-5 ccs. of blood was allowed to clot.

Urine was collected over 24 hours in Winchester bottles, toluol being used as the preservative, but where incontinence or other conditions made a 24 hour collection impossible, 6 ounce screw-capped bottles were used. The latter bottles were also used to collect the residual urine from the bladder immediately after death.

Cardiac puncture was performed on all patients who had died. The needle was introduced in the third or fourth left interspace close to the sternal border and introduced slowly until the lessening resistance indicated that it was within the cardiac chamber.

Immediately a sample of blood and urine had been collected it was taken to the laboratory, where the following procedure was carried out:-

BLOOD.

a. The 15 cc. pyrex tube was put in the centrifuge and spun at 3,000 r.p.m.

b. The blood in the specimen bottle was gently stirred with a clean glass rod, and 0.1 ml. withdrawn for the determination of lactic acid. This was immediately treated with copper sulphate and calcium hydroxide in order to stop glycolysis, and the sample stored in the refrigerator.

c. The sample in the centrifuge had now been spun for about 10 minutes. The supernatant plasma was then pipetted off into a clean dry test tube.

The estimation of bicarbonate was commenced, and while the plasma was being brought to normal alveolar carbon dioxide tension in the separating funnel, two ccs. of plasma were treated with trichloracetic acid in preparation for the phosphorus determination.

The plasma bicarbonate estimation was then completed.

The remaining determinations could be performed with more leisure, although it was usual to carry out the oxygen unsaturation and haemoglobin within the next two hours. Although the inactivated blood for lactic acid determination could be kept safely in the refrigerator for 24 hours, it was usual for it to be estimated as soon as possible after withdrawal.

The not-so-urgent determinations were often racked until four or five had accumulated, and by so doing, time and labour were saved and accuracy still maintained. These included phosphorus (the protein having been precipitated, and the filtrate collected), urea, bilirubin and calcium.

URINE.

The routine adopted with urine determinations followed a similar plan, the pH, ammonia and titratable acidity being done immediately, while the chloride was usually estimated in batches along with other samples some time later.

Reagents and Apparatus.

All the biochemical estimations were done personally after a sufficient number of 'normals' showed that proficiency in a method and standardisation had been attained.

The reagents used were either made up professionally by a firm of manufacturing chemists, or else were the standard reagents used from day to day in the biochemistry department of the hospital. These were always checked from time to time as required, and correction factors applied.

Glass ware was kept scrupulously clean, being scrubbed and washed in hot water after every experiment. It was then finally dried in an electric oven. The aim was to use each pipette for one reagent only, but where this was impossible, pipettes were flushed with water through a pump and dried by a final application of acetone before being used.

From time to time, all glass ware was cleaned in a bath of sulphuric acid - chromic acid mixture.

Detailed notes on the methods used have been relegated to the Appendix because their inclusion at this point is not necessary to the continuity of the thesis.

Plan of Collection of Blood and Urine from Patients.

No rigid plan of collection of samples could be applied to all patients, because it was impossible to predict the date of death. The general aim, however, was first to record the blood and urine biochemistry of a patient while he was relatively well. This was easy to do in patients suffering from such diseases as bronchial carcinoma or tuberculous meningitis in the very early stages, or soon after a cerebral haemorrhage, but in pulmonary tuberculosis the patient's general condition had already deteriorated considerably before indications that his disease would be fatal were obvious.

Having made this first record, the duration of life was approximately predicted, and if long, no further estimations were made until the clinical pre-terminal state was reached. Estimations were then done daily or every second day until death occurred, when the final estimations were made.

Two complete blood estimations, and rarely three could be done during the 24 hours, but any more than this was impossible due to the fact that the author was working single-handed, and because routine hospital duties lessened the time available for laboratory work.

Cardiac puncture was performed as soon after death as possible and in most cases it was possible to collect the blood within a matter of minutes, but inevitably the time varied and this is indicated on the individual case records. In no case did it exceed 12 minutes.

CHAPTER V.

THE THEORETICAL CONCEPTION OF THE AGONAL STATE - I.

Before proceeding to analyse the results obtained in the present series, it is first necessary to examine the various methods by which the body deals with changes in its finely adjusted internal environment.

It is known that the human body can withstand great metabolic changes by adjustments between the various electrolyte constituents, and it is probable that normal cellular metabolism can also be altered, at least temporarily, to meet the needs of a low oxygen supply. Glycolytic function, on the other hand, does not seem to be appreciably affected by acidosis per se (Gilchrist, 1932).

Changes in the Acid-base Equilibrium.

The defences against acidosis comprise the buffer action in the blood and tissues, and the excretory functions

of the lungs and kidneys.

Of the buffer actions, the following are important:

a. Carbonic Acid - Bicarbonate. It is the ratio of free carbonic acid to bicarbonate which regulates the activity of the respiratory centre. Any change which results in the amount of free carbon dioxide becoming relatively greater than that of the combined carbon dioxide will stimulate the centre to greater activity.

Excess acid (HA) would be dealt with in the blood according to the following equation:-

$$HA + BHCO_3 \rightleftharpoons BA + H_2CO_3$$

The decrease in $BHCO_3$ and the increase in H_2CO_3 upsets the normal ratio $\frac{H_2CO_3}{BHCO_3} = \frac{1}{20}$, thereby stimulating the respiratory centre and leading to excretion of the excess carbon dioxide. The ratio $\frac{H_2CO_3}{BHCO_3}$ is thus returned to normal.

With obstruction to the escape of carbon dioxide from the alveoli, there is an increase of carbon dioxide in the blood. Of the two forms in which carbon dioxide occurs in the blood, the $B \cdot HCO_3$, which is dependent on residual base and renal control, is the more fixed, and so the increase is relatively greater, at least at first, in the $H \cdot HCO_3$ fraction, with a disturbance in the 1 : 20 ratio.

As pH is equal to $6.1 + \log \frac{H \cdot HCO_3}{B \cdot HCO_3}$, the increase in

$H \cdot HCO_3$ causes a reduction in pH and an uncompensated acidosis.

To compensate, there needs to occur an increase in $B \cdot HCO_3$ which could be made possible by renal elimination of chloride, permitting accumulation of $B \cdot HCO_3$ and return of the $\frac{H \cdot HCO_3}{B \cdot HCO_3}$ buffer system to the normal ratio of 1 : 20 (Spector & McKhann, 1948).

b. Plasma Proteins. The proteins of the blood are amphoteric, and are combined with either base or acid. The addition of acid therefore causes a reaction with the base bound protein:

$$HA + BPr \rightleftharpoons BA + HPr$$

This liberates a certain amount of base and at the same time converts a strong acid HA into a relatively weak acid HPr.

Campbell & Poulton (1920) state that throughout the range of pH occurring in the body, all the carbon dioxide is present as bicarbonate, and the blood proteins act as acids combining with sodium and competing for it with the carbon dioxide.

c. Phosphates. The buffer action of the acid and alkaline phosphates provides a nice example of the delicate mechanism provided for the regulation of acid-base balance. It is a minor mechanism, however, due to the small amount of phosphate present.

The reaction can be represented thus:

$$HA + Na_2HPO_4 \leftrightharpoons NaH_2PO_4 + NaA$$

Besides quickly buffering the acid, the acid phosphate is rapidly excreted by the kidneys.

d. Haemoglobin. At the normal reaction of the blood, haemoglobin acts as a weak acid. Reduced haemoglobin, according to Graham & Morris (1933), is an acid sixty-seven times less dissociated than oxyhaemoglobin, and the amount of base set free during the reduction of oxyhaemoglobin has been calculated to be sufficient to combine with four-fifths of the carbon dioxide given off during the resting state.

Haemoglobin is an important buffer because of its amount, and it is well known that acidosis is a much more severe condition in an anaemic patient.

e. The Hamburger Phenomenon. If the carbon dioxide tension of whole blood is raised, the chloride of the plasma decreases, the chloride of the corpuscles increases, and the plasma bicarbonate increases.

The mechanism by which this occurs can be explained as follows:-

The corpuscular membrane is permeable to the anions Cl^- and HCO_3^-, but is impermeable to the kations Na^+ and K^+. When carbon dioxide enters the blood from the tissues there is a small increase in the H_2CO_3 content of the plasma, and

a large increase in the corpuscles (owing to the presence of carbonic anhydrase). In the corpuscles the H_2CO_3 reacts with the haemoglobin thus:

$$H_2CO_3 + KHb \rightarrow KHCO_3 + HHb$$

The bicarbonate in the cells is now in greater concentration than in the plasma, and therefore migrates out, and Cl^- moves into the cells to restore the normal cell/plasma relationship of HCO_3^- and Cl^- (Wright, 1940).

Outside the buffering action of the proteins and phosphates of the blood, the extent of the chloride shift and the amount of haemoglobin present would seem to determine the possible degree of compensation of acidosis (Myers & Booher, 1924).

The efficiency of the above buffering systems are at their maximum when the contents of salt and acid are equal. Graham & Morris (1933) give the following table showing the pH values at which the buffering systems contain equal amounts of the two factors, and therefore at which the buffers are most efficient:

H_2CO_3	: $BHCO_3$	pH	6.1
BH_2PO_4	: B_2HPO_4	"	6.8
$HHbO_2$	: $BHbO_2$	"	7.16
HHb	: BHb	"	7.3

It is seen that the lower the pH falls, the more efficiently do the buffers function.

Along with an efficient buffering system, it is also necessary that the function of the respiratory system and the kidneys be intact, since the end products of the buffering action are carbon dioxide, which is disposed of by increased respirations, and acid salts which are excreted in the urine.

The bowels and skin play very little part in the acid base regulation (Graham & Morris, 1933).

The Urine.

In the acidotic state, the pH of the urine falls, and certain mechanisms come into play.

The weaker acids, which have pH values above 4.5 are excreted as free acids, thus conserving base.

Stronger acids are excreted immediately by utilising the base from the bones, namely Calcium and Phosphorus, and Sodium and Potassium from the tissues.

Benedict & Nash (1929) demonstrated the rôle of ammonia in the excretion of acid by the kidneys. Ammonia is formed in the kidneys themselves, and by combining with the acids, which are excreted as ammonium salts, valuable tissue base is thereby spared. The ammonia mechanism does not function immediately, but takes several days to reach its peak.

In health, only 3 to 5 per cent. of urinary nitrogen is excreted in the urine as ammonia, whereas in acidotic conditions this figure may rise to 20 per cent. Thus the increase of ammonia in the urine is a measure of the amount of excess acid to be neutralised.

The Rôle of Chloride.

It is said that the level of plasma chloride rarely varies except within the normal range of 560 to 650 mgms. per cent. Trumper & Cantarow (1932) state that withdrawal of salt from an otherwise normal diet rarely lowers the chloride to below the lower limit of normal.

In a fasting individual, however, it may fall below normal due in part to the sodium chloride deprivation, but also because of acidosis, causing the chloride shift from plasma to corpuscles.

The importance of the Hamburger Phenomenon in acid base regulation has been stated. The migration of the chlorine ion from plasma to corpuscles in states of acidosis will therefore cause a lowering of plasma chloride.

This in fact occurs, according to Graham & Morris (1933) in non-gaseous acidosis, but they point out that if there is great loss of water and base as in diarrhoea, or dehydration from other causes, the plasma chlorine will be increased.

Gaseous acidosis also causes a low plasma chloride because of the large shift of chlorine to the corpuscles.

A well known physiological phenomenon is the alkaline tide by which there occurs a mild temporary alkalosis due to the secretion of chlorine as free hydrochloric acid in the gastric juice (Brunton, 1933).

In general, there is a reciprocity between the levels of chloride and carbon dioxide in the blood which tends to keep the ionic concentration constant. This rule, however, does not always hold, for instance in diabetic acidosis, the carbon dioxide and chloride fall together. Also, in the acidosis of chronic nephritis the alkali reserve is low and so also is the chloride. Graham & Morris suggest that when the blood urea rises in the latter condition, the chloride falls in order to keep the osmotic pressure normal.

Ambard (1920) showed that in health there was some relationship between the level of plasma chloride and the urinary excretion of chloride, but this does not seem to hold good in disease, for both in diabetes and chronic nephritis chloride excretion continues after the plasma chloride has reached very low levels.

Stewart & Dunlop (1930) showed that in subacute parenchymatous nephritis, the concentration of chloride in the urine is very considerably decreased, and in severe cases may be practically free of chloride.

In lobar pneumonia, chloride practically disappears from the urine; many theories have been advanced to explain this phenomenon, but it is probable that the true scientific explanation has still to be found.

The Types of Acid Base Disturbance.

Haldane's classification is in common use, and his four headings give a good indication of the physical changes causing the abnormal deviation.

a. Non-gaseous Acidosis.

The primary change is a fall in the $BHCO_3$ with a smaller secondary fall in the H_2CO_3 , and is characterised by a fall in pH and an increase in respiration in order to get rid of excess carbon dioxide so that the ratio $\frac{H_2CO_3}{BHCO_3}$ is brought to the normal 1 : 20.

b. Gaseous Acidosis.

The primary change is a rise in the free carbon dioxide with a smaller consequent rise in $BHCO_3$ in order to conserve the ratio $\frac{H_2CO_3}{BHCO_3}$ at 1 : 20. The pH of the blood falls and the total carbon dioxide rises. An example of such a state is the paralysis of the respiratory centre by morphine poisoning.

Of less interest in the present survey of pre-agonal changes are the remaining two types:

c. Non-gaseous Alkalosis, in which there is a primary rise in the combined carbon dioxide, and

d. Gaseous Alkalosis, in which there is a primary diminution in free carbon dioxide.

Figure 2, adapted from Van Slyke (1921), illustrates

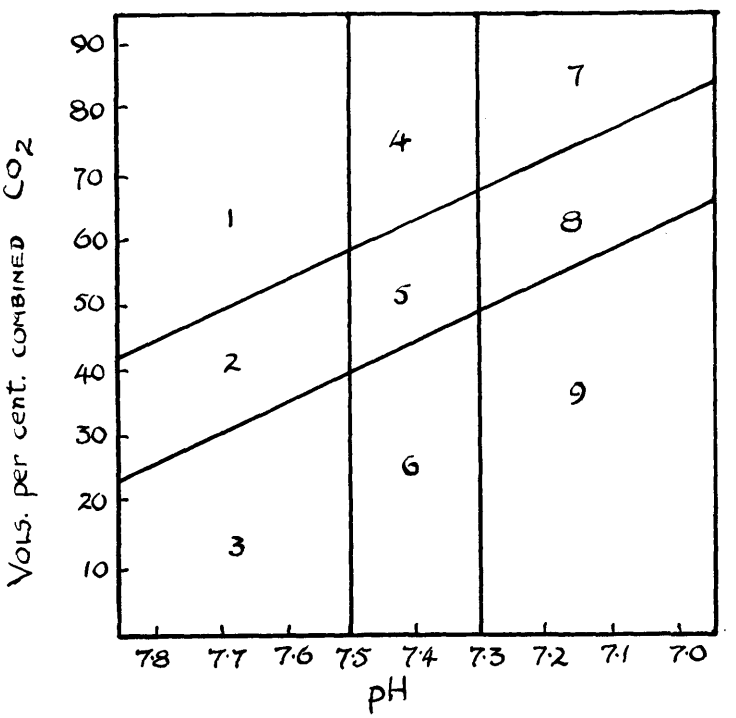


Figure 2.

graphically the variations from normal which may occur. He makes use of the terms compensated and uncompensated, which in effect mean that the blood pH is normal or either below or above normal. For example, a compensated alkali deficit would mean that the combined carbon dioxide was diminished, while the pH remains normal (Figure 2, No. 6).

Graham & Morris point out that the pH in fact always changes, but sometimes so slightly that it cannot be detected by the rather crude methods of measurement in use.

Gaseous Exchange.

In the chapter dealing with the clinical features of the dying patient it was pointed out that one of the most constant alterations was in respiration, whether the patient was suffering from a pulmonary or cardiac lesion or not. The stages passed through are in order: normal breathing, followed by increased respirations, and finally slow irregular gasping respirations.

It might be reasonably assumed that the normal gaseous exchange in the lungs would be interfered with, producing carbon dioxide retention, and oxygen deprivation.

1. Carbon Dioxide.

Carbon dioxide retention has already been considered under the heading of gaseous acidosis.

Davies, Haldane & Priestley (1919) investigated the changes which took place in respiration when there was a resistance to the free flow of air to the lungs.

The net result was that breathing became deeper and slower, being the normal response to such resistance.

When the resistance was excessive or the respiratory centre became fatigued or weakened by anoxaemia, a particular

phenomenon occurred - the breathing became shallower and more frequent. The authors considered that this throws a new light on failure of the respiratory centre as a common - perhaps the commonest - immediate cause of death.

Anoxaemia hastens greatly the onset of fatigue and the ease with which it is produced. This explains the characteristic action of anoxaemia in producing relatively shallow and frequent breathing. As shallow breathing is in itself both a result and a cause of anoxaemia, a vicious circle of a very dangerous kind is apt to be produced by anoxaemia or any other cause which tends to impair the vigour of the respiratory centre.

The resistance in the experiments carried out by Davies, Haldane & Priestley was provided by tightly packed cotton wool in the airway of the breathing mask, but pathologically may include any obstructive condition, weakness, or paralysis of the muscles of respiration.

The condition of course becomes even more dangerous if the respiratory centre is also impaired by toxaemia.

Newburgh, Means & Porter (1916) showed in dogs that pneumonia diminished the sensitivity of the respiratory mechanism to carbon dioxide, and that the greater the severity of the disease the less the sensitivity.

The effect of shallow breathing on the oxygen saturation of the blood has also been investigated by Meakins

and Davies (1920). They found that the oxygen saturation of arterial blood fell from 94.3 per cent. to 91.7 per cent. when the respiratory rate was increased from 17.5 per minute to 48 per minute.

Thus the analogy with the state of affairs present in the immediate pre-agonal period in seen; the effect of oxygen want in increasing the sensitivity of the respiratory centre to carbon dioxide acts only up to a certain point, after which the respiratory centre and the muscles of respiration fail.

The consequences of carbon dioxide retention have been studied by various workers. Davies, Haldane & Kennaway (1920) found that breathing a moderate excess of carbon dioxide (about 6%) for two hours produced little if any change in the carbon dioxide capacity of the blood. There was, however, diuresis, increased urinary acidity and increased ammonia excretion in the urine.

Jacobs (1920) performed experiments to show that dissolved carbon dioxide possesses a higher power of penetrating the cell wall than has sodium bicarbonate. He demonstrated that a condition of intracellular acidity can be produced by a slightly alkaline solution of carbon dioxide in M/2 sodium bicarbonate almost as effectively as by a solution of carbon dioxide in distilled water, although the cH of the latter

solution is approximately 4,000 times as great as that of the former. Thus the forcible retention of carbon dioxide in the blood will have a much more profound effect on the pH of the cells than fixed acid in the blood.

The clinical appearance of a subject who suffers from oxygen lack and retention of carbon dioxide together is of deep plum colour or purplish cyanosis, as in strangulation. On the other hand, when there is oxygen lack associated with a normal or diminished carbon dioxide content of the arterial blood, there results a depression of the vasomotor centres giving a greyish pallid cyanosis. This indicates an impending respiratory and an actual circulatory collapse. Both are due to deficiency of the carbon dioxide stimulus. This has been experimentally shown in animals by Dale & Evans (1922).

The grey, pallid cyanosis is typical of the immediate pre-agonal period when respiration is irregular and slow with long periods of apnoea. At this point oxygen deficiency is becoming severe.

Recently, Simpson (1948) studied the effect of breathing excess carbon dioxide in human subjects in relation to the pressure of cerebrospinal fluid. In all cases there was a rise in cerebrospinal fluid pressure. Wolff & Lennox (1930) obtained similar results in animals. It is unlikely that

this has any relation to the mechanism of death.

2. Oxygen.

When the arterial blood reaches the capillaries, the oxygen is in the form of oxy-haemoglobin, with a small amount in physical solution which at body temperature, according to Meakins & Davies (1925) is about 0.24 ccs. in 100 ccs. of blood. The tissues acquire this oxygen as follows: first, as the blood passes through the capillaries, the tissues take up some of the oxygen which is in physical solution, and consequently the partial pressure tends to fall. However, the oxy-haemoglobin, by giving up oxygen in accordance with its dissociation curve prevents this falling too far. It is probable that these two processes are synchronous.

The dissociation curve of the oxy-haemoglobin of arterial blood is influenced by several factors, namely increase in carbonic acid and lactic acid, and increase of temperature that occurs in the capillaries as a result of tissue oxidation. These factors all tend to lower the dissociation curve of oxy-haemoglobin, and as a result, oxygen will be more readily given up to plasma to provide a continuous diffusion of oxygen to the tissue fluids, lymph and cells.

Death of the cells of the body is always due, in last analysis, to interference with oxidation, whether this is brought about by lack of oxygen, by the presence of substances which interfere with oxidation or by mechanical injury.

Barcroft (1920) observed that "Anoxaemia not only stops the machine, but wrecks the machinery."

Koehler, Behneman, Benek & Loevenhart (1925) devised experiments on pigs to ascertain the effect of anoxaemia on the bodily functions. This work has been referred to in previous chapters and is now discussed more fully.

They demonstrated the acidotic nature of anoxaemia and this suggested to them the possibility that acidosis per se might be the cause of death. They set out to study the degree of acidosis existing at the time of death, the rate of recovery from it and whether there is a certain degree of acidosis produced by anoxaemia which is compatible with recovery.

The results were as follows. The blood reaction during sufficiently severe anoxaemia and during the recovery process is diphasic. In response to anoxaemia the blood shows in the first place a phase of alkalosis, due to the excessive loss of carbon dioxide during hyperpnoea. This first phase has also been demonstrated in humans at high altitude by Haldane, Kellas & Kennaway (1919), who found a great diminution of the total acid and ammonia normally excreted in the urine.

In the pig experiments there followed a phase when the fixed acids, produced as a result of decreased oxidation in the tissues of the body, compensate for the loss of carbon dioxide,

and the blood pH becomes normal. Following this there developed a most extreme grade of acidosis, depending on the degree and duration of reduced oxidation (Figure 3). On restoring the animal to normal atmosphere, the coma and distress of reduced

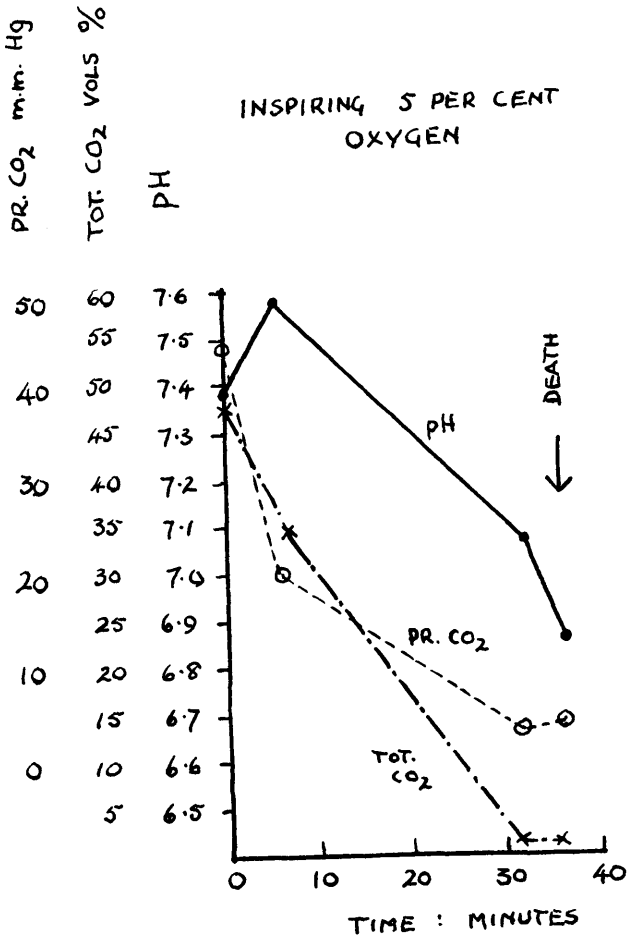


Figure 3.

oxidation rapidly disappeared and there followed a marked increase of the pH of the blood.

In order to determine the part played by the acidosis in the symptomatology of oxygen want, the authors injected a

3 per cent. sodium bicarbonate solution intravenously into a series of animals after anoxaemia and acidosis had occurred. They found that this procedure greatly prolonged the life of the animals - approximately 2.5 times as long as the controls.

It is known that acidosis is unfavourable to oxidation, and it would seem that a vicious circle is being set up when decreased oxidation causes acidosis, and acidosis further decreases oxidation, thereby making it more difficult for the tissues to utilise even the reduced amount of oxygen which is available. The administration of alkali did seem to have some effect in breaking this circle.

Koehler and his co-workers found that the total carbon dioxide levels during anoxaemia were very low, one level being as low as one volume per cent. This decrease, they say, was due to loss by hyperpnoea and neutralisation of blood alkali by non-volatile acids.

From experiments in vitro, Evans (1922) found that 10 mgms. of lactic acid added to 100 ccs. of blood occasions a fall in carbon dioxide of 1.5 vols. per cent., but Jervell (1928) states that in vivo the average fall of alkali reserve with an increase of 10 mgms. per cent. blood lactic acid is 2.65 - 3.98 vols. per cent.

The response of the cardio-vascular system to anoxia was studied by Gilbert & Greene (1921). They found that a constant effect was tachycardia, which changed in the terminal stages to severe bradycardia. There was also an exaggerated sinus arrhythmia.

In animals, it was found that anoxia caused prolongation of the PR interval, and in some cases led to heart block. This effect was also demonstrated in humans in several instances.

CHAPTER VI.

THE THEORETICAL CONCEPTION OF THE AGONAL STATE - II.

Cellular Respiration.

From clinical observation, it has been assumed that oxygen lack plays a major part in the mechanism of death, especially in the last few hours of life when, as has been shown, respiration is greatly deranged.

It is necessary now to consider the effect of anoxia on the metabolism of the body cells in the light of previous experimental work on this subject.

Pasteur (1876) had noted that oxygen gas inhibits fermentation, and that cells become fermentative when their vital action is protracted in the absence of air.

Most studies on anaerobic metabolism have made use of yeast and muscle, and it has been found that both derive the energy they expend through very similar manipulations of their carbohydrate starting materials, and both are relatively easy to work with.

According to Baldwin (1947) there is now evidence that tissues other than muscle, such as liver, kidney, brain, etc., make use of reactions which are essentially the same as those employed in muscle.

In the following paragraphs it is proposed to set forth the accepted theories of anaerobic metabolism as briefly as possible.

Yeast juice was found to be capable of converting glucose into ethyl alcohol and carbon dioxide:

$$C_6H_{12}O_6 = 2CO_2 + 2\ CH_3CH_2OH$$

The rate of fermentation, however, begins to fall off, but can be restored by adding inorganic phosphate to the mixture. As soon as the concentration of free phosphate declines the rate of fermentation slows.

The disappearance of free phosphate from the fermenting system indicates that phosphate esters are being formed, and this was in fact shown to be the case, the substance being hexose diphosphate. Later, other esters were also discovered.

Adenosine triphosphate acts as a phosphate carrier - a co-enzyme which has the power of transferring its phosphate radicle to other substances, so forming a chain of the fermentation reaction. In the cycle of events, adenosine

triphosphate is eventually re-synthesised.

So, it is demonstrated that phosphate is indispensible in the fermentation reaction.

Turning to muscle. It is known that muscle can contract in a perfectly normal manner in complete absence of oxygen, but lactic acid is produced, and accumulates with continued stimulation until in the end the muscle becomes fatigued.

If the fatigued muscle is then put into oxygen, it recovers its ability to contract, and lactic acid simultaneously disappears.

Phosphates play an important part in muscle glycolysis, just as in yeast fermentation, and the important co-enzyme is creatine phosphate (phosphagen), but adenosine triphosphate is also present, and in the production of lactic acid from glycogen by enzymes and co-enzymes, both are broken down.

Figure 4 illustrates in tabular form the currently accepted scheme of glycolysis as depicted by Gemmill (1939).

1. Glycogen + phosphate	⇌	glucose - 1 - phosphate
2. Glucose - 1 - phosphate	→	glucose - 6 - phosphate
3. Glucose - 6 - phosphate	⇌	fructose - 6 - phosphate
4. 2 Hexone - 6 - phosphate + adenosine triphosphate	⇌	adenosine triphosphate + 2 hexose -1-6-diphosphate
5. Hexose - 1 - 6 - diphosphate	⇌	2 triosphosphate
6. dihydroxyacetone phosphate	⇌	3 - glyceraldehyde phosphate
7. Triosephosphate	⇌	3 - phosphoglycerate
8. 3-phosphoglycerate	⇌	2 - phosphoglycerate
9. 2-phosphoglycerate	⇌	phosphopyruvate
10. Phosphopyruvate	→	pyruvate - phosphate
11. Pyruvate	⇌	lactate

Figure 4.

The reactions concerned in glycolysis are very similar to those in fermentation until the pyruvic acid stage is reached. In yeast, pyruvic acid is split into carbon dioxide and acetaldehyde in the presence of carboxylase, but in muscle no carboxylase is present and pyruvic acid itself discharges this function and is reduced to l-lactic acid.

It is not thought necessary to delve too deeply into the intricacies of microbiology and discuss at length the biochemistry of adenosine triphosphate and phosphagen, and it is sufficient to say that inorganic phosphorus plays an important part in the energy production of the living cell when sufficient oxygen is available for respiration. On the other hand, when the tissue cells are deprived of oxygen there is a breakdown of hexose phosphate according to Meyerhof's equation, with formation of equivalent quantities of phosphorus and lactic acid.

Franks, Berris, Kaplan & Myers (1948) found that in almost every case of diabetic acidosis the plasma inorganic phosphorus was raised above normal, and that it fell precipitously after the administration of insulin. They could not, however, correlate the level of plasma phosphorus with the severity of the acidosis and concluded that the phosphorus, which has an important intermediary rôle as a reservoir of energy is set free because of lack of insulin, but is immediately taken up again for the phosphorylation of glucose when insulin is injected.

The fate of lactic acid and inorganic phosphorus, the two substances which have been chosen for study in the present investigation, may be mentioned briefly.

Some of the free phosphate is used again in the various reactions of phosphorylation, but in a persistent state of anoxaemia it is conceivable that the level of free inorganic phosphorus will continue to rise.

Cori & Cori (1936) have shown that any lactic acid formed in mammalian muscle in situ diffuses out and is carried by way of the blood stream to the liver. There, in the presence of sufficient oxygen it is oxidised and phosphorylated and built up into liver glycogen by reversal of the glycolytic sequence. In the absence of sufficient oxygen, the blood lactic acid will rise.

Aerobic Metabolism.

Only a word need be said regarding aerobic metabolism, in order to make the picture complete.

According to Baldwin (1947), lo lactic acid need be formed at all, and instead it might be anticipated that pyruvic acid would accumulate in the muscle. There is no such evidence that it does, nor is there any evidence that much pyruvic acid escapes from the muscle into the blood.

The conclusion is then that if pyruvic acid is formed under aerobic conditions, it must be oxidised and that it is the source of much or all of the carbon dioxide produced by an active muscle.

Pyruvic acid then, occupies an important position in the metabolism of carbohydrate. It can be formed either from glucose (after phosphorylation) or from glycogen (after phosphorolysis) by the normal reactions of glycolysis.

CHAPTER VII.

THE AUTHOR'S INVESTIGATIONS.

The present series comprises 50 patients, 30 of whom are male, and 20 female.

The number of patients in each age group is shown in Figure 5.

Age Group	0-20	21-30	31-40	41-50	51-60	61-70	71-80
No. of Patients	5	14	11	12	6	1	1

Figure 5.

A classification of the diseases from which the subjects died is recorded in Figure 6.

Diseases	No. of Cases
Respiratory Diseases:	
1. Pulmonary Tuberculosis	27
2. Bronchial Carcinoma	6
Diseases of the Alimentary System:	
1. Tuberculous enteritis	2
2. Carcinoma of the pancreas	1
Diseases of the Central Nervous System:	
1. Cerebral Haemorrhage and Thrombosis	2
2. Tuberculous Meningitis	2
3. Transverse myelitis	1
Diseases of the Heart:	
1. Congestive Cardiac Failure	5
Combined Diseases:	
1. Tuberculosis of Lungs & Intestines	2
2. Tuberculosis of Lungs & Meninges	2

Figure 6.

Control estimations were done on six subjects at various times during the series, the blood and urine being collected from healthy patients about to be discharged from hospital, and from colleagues.

In order to compare the readings with the agonal cases, estimations were also carried out on three patients, one with severe renal damage who died, and two with congestive cardiac failure who recovered.

Complete blood and urine examination was not carried out in all patients of the series. As explained previously, individual biochemical estimations were added from time to time as the series grew in the light of experience gained, and others were dropped. In many cases it was impossible to utilise the urine for pH, ammonia and titratable acidity determinations because of gross infection.

The total number of estimations made, excepting the controls and illustrative cases, is tabulated in Figure 7.

BLOOD			
Plasma bilirubin	100	Serum calcium	19
Plasma bicarbonate	131	Plasma proteins	23
Oxygen saturation of venous blood	76	Blood urea	88
Plasma chlorides	121		
Plasma phosphorus	121	URINE	
Blood lactate	69	pH	150
		Ammonia & titratable acidity	107
		Chlorides	108

Figure 7.

a. Plasma Bicarbonate.

Panton & Marrack (1927) give the following range of values for plasma bicarbonate in the normal state and varying degrees of acidosis:

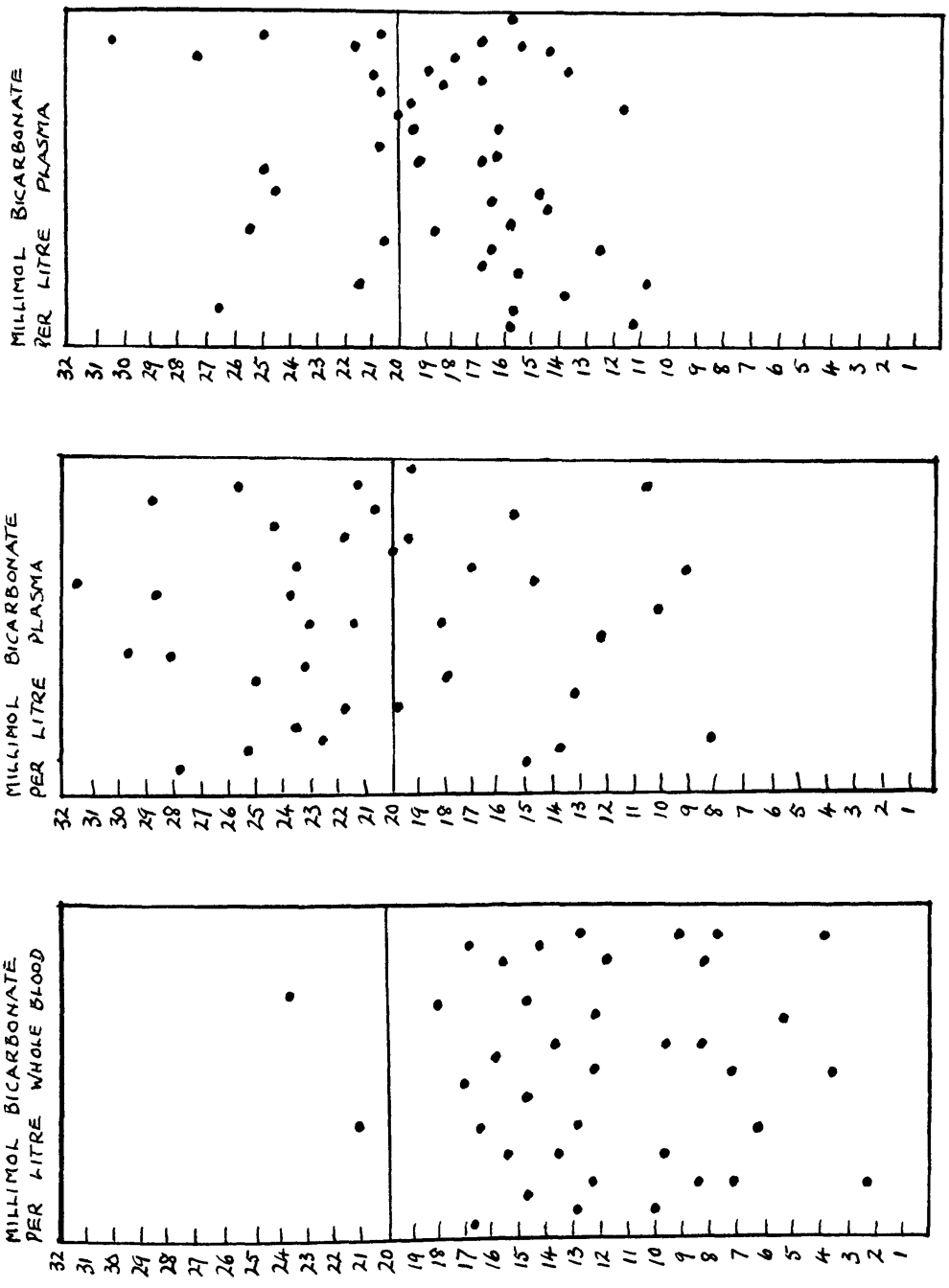
Normal	55 - 70	vols. carbon dioxide per cent.
Slight acidosis . .	45 - 55	" " " " " "
Moderate acidosis .	30 - 45	" " " " " "
Severe acidosis . .	under 30	" " " " " "

The plasma bicarbonate was determined at death in 46 patients of the present series, the mean value being 41 vols. carbon dioxide per cent. or 18.3 m.eq. per litre.

Hansen (1948) in his series of 38 cases found a mean value of 20.5 m.eq. per litre. In 15 of his 38 cases, the bicarbonate concentration was decreased to less than 20 m.eq. per litre, and he concluded that an excessive reduction of plasma bicarbonate rarely occurs at death.

Whitney (1917) made bicarbonate determinations on an unselected series of patients and found acidaemia in 36 out of 40 cases; of these, 29 showed a fall in blood bicarbonate to less than 15 m.eq. per litre.

Hansen made a comparative scattergram showing the difference between his own series and that of Whitney's. These are reproduced in Figure 8 and a third graph drawn to the same scale is added showing the distribution of values in the author's series.



Author's Cases.

Hansen's Cases.

Whitney's Cases.

Figure 8.

A comparison between the graphs shows that the figures in the present series tally more closely with those of Hansen, although the mean value for plasma bicarbonate is slightly lower, and the bulk of the values, 55 per cent., are below 20 m.eq. per litre, whereas only 39 per cent. of Hansen's cases had values below 20 m.eq. per litre.

On the other hand, the mean value of plasma bicarbonate in Whitney's series is much lower than in either Hansen's or the author's series.

Several factors may be responsible for Whitney's low results:-

1. Although he excluded cases of diabetic coma, there were included in his series 5 cases in which renal function was obviously impaired;

2. There were six cases of pernicious anaemia, and some gave particularly low bicarbonate values. It has been pointed out in a previous chapter that haemoglobin is an important buffer of the blood because of its amount, and that acidosis in an anaemic patient is a much more severe condition.

3. Whitney used whole blood to determine the bicarbonate concentration bringing it to a tension of 40 mms. of mercury. It is known that the carbon dioxide tension of erythrocytes is slightly lower than that of plasma.

To explain the higher values in his own cases compared with those of Whitney's, Hansen mentions the factors set out above, and also suggests that treatment aimed at correcting the acidosis in 11 of his cases might have had some effect in raising the mean value, although he points out that there was no significant difference between the mean bicarbonate value of the 11 treated cases (21.5 m.eq. per litre) and the remainder (20.2 m.eq. per litre).

In all Whitney's cases, bicarbonate estimations were done on blood taken after death, as in the author's series, whereas in 7 of Hansen's cases, the blood used for estimation was withdrawn by venepuncture within 24 hours of death.

The mean value of these cases works out at 22.2 m.eq. per litre and therefore has some effect in raising the mean value of the whole series.

In the author's series, blood from 17 cases was examined within 24 hours of death giving a mean bicarbonate value of 18.7 m.eq. per litre compared with 18.3 m.eq. per litre at death for the whole series of 46 cases. The difference is not significant.

Hansen attempted to relate the degree of acidosis to certain diseases or group of diseases, but a review of his case records did not reveal any such relation, and he

concluded that the acidosis in the patients he examined was a common agonal phenomenon.

In the author's series, a similar attempt was made to relate the level of plasma bicarbonate at death with groups of diseases, the results being shown in Figure 9.

Diseases	Vols. CO_2%	m.eq. per litre	No.of Cases
Pulmonary	41.1	18.3	30
Alimentary	32.3	14.3	3
Central Nervous System	47.6	21.2	6
Cardio-vascular System	36.8	16.4	5
Combined diseases	45.0	20.0	2

Figure 9.

It will be seen that the lowest values were recorded in patients dying of gastro-intestinal disease. The number of cases is small and in each the lesion was tuberculous ulceration of the intestines with frequent passage of loose stools. The loss of base in such cases with prolonged diarrhoea is considerable and no doubt is the reason for the very low bicarbonate values.

In the 5 patients who died of congestive cardiac failure, one of them also suffering from subacute bacterial endocarditis, the mean bicarbonate value at death was 16.4 m.eq. per litre, which is considerably below the lower limit of normality. Conflicting views as to the behaviour of the plasma bicarbonate in congestive cardiac failure appear in the literature.

Campbell, Hunt & Poulton (1923) found that there was no great change from the normal limits of carbon dioxide combining power in auricular fibrillation and other forms of tachycardia unless conspicuous signs of cardiac failure had developed, in which case it was low.

On the other hand, Meakins & Davies investigating cases of circulatory failure with venous congestion found the carbon dioxide combining power to be slightly raised if anything, and attribute this to the fact that most of their cases had emphysema, the cardiac failure being secondary.

After studying a number of cases of cardio-renal disease, in which dyspnoea was a marked feature, Lewis, Ryffel, Wolf, Cotton & Barcroft (1913) came to the conclusion that acidosis was a constant feature, although they failed to demonstrate the presence of lactic or other abnormal acids in the blood.

Peters & Barr (1920-21) came to the conclusion that cardiac decompensation is sometimes associated with a real reduction of the alkali reserve of the blood, which disappears when compensation is re-established. The findings in Cases A and B listed in the Appendix to this thesis tend to confirm Peters & Barr's view.

Although the total carbon dioxide content of the blood may be raised in a case of recent congestive cardiac failure due to carbon dioxide retention and increase in carbon dioxide tension, it is suggested, from the figures available in the present cases, that the plasma bicarbonate, estimated after being brought to normal alveolar carbon dioxide tension, will fall far below normal, especially at death and after a prolonged illness.

It will be shown in a following chapter that the co-existing anoxaemia induces a great rise in acid metabolites, especially lactic acid, which in turn have a profound effect in lowering the level of the plasma bicarbonate.

In the 30 cases dying of pulmonary lesions the mean plasma bicarbonate reading at death was 18.3 m.eq. per litre, which was in fact the mean for the whole series.

The bulk of the patients were suffering from pulmonary tuberculosis, and the majority of these had a prolonged illness.

This moderate fall in plasma bicarbonate is in agreement with the findings of Hansen, who also included

many cases of pulmonary tuberculosis in his series.

Dautrebande & Davies however state that they found an average increase of 9 vols. per cent. in the alkali reserve of 7 cases of extensive pulmonary tuberculosis. They do not state whether the patients were moribund or whether their disease was controlled, and it is considered that without this information, no conclusions can be drawn, which can be used as a comparison with those of the present series.

Several cases in the author's series died with an artificial pneumothorax which had been induced and re-filled during the illness. It is not considered likely that this affected the plasma bicarbonate to any significant degree, although Meakins & Davies (1923) showed experimentally that by collapsing a diseased lung by artificial pneumothorax, a compensated gaseous acidosis, such as occurs in emphysema, could be converted into a compensated non-gaseous alkalosis, due to shunting of blood from the diseased to the sound lung. In these experiments they also found that the urine changed from an acid to alkaline reaction, and that the kidneys ceased to form ammonia.

Packard, Hayes & Blanchet (1940) state that observations on the gaseous content of arterial blood in cases of pulmonary tuberculosis with unilateral pneumothorax indicate that the blood is normally saturated with oxygen and that

there are no significant variations in the carbon dioxide content.

It is probable that Meakins & Davies (1925) were unable to demonstrate the blood and urine changes in their cases because at the time their experiments were performed, artificial pneumothorax was completed quickly, usually within 24 hours, whereas the modern method is to collapse the lung gradually by small re-fills over a number of weeks.

The mean reading of 21.2 m.eq. per litre found in the 6 cases dying from diseases of the central nervous system is the highest for the five groups listed. In four of the patients the duration of illness was short compared with those dying of pulmonary tuberculosis or carcinoma of the bronchus. Two had cerebral haemorrhage and died within a few days of the onset; two had tuberculous meningitis, dying within 21 days of onset, One patient had pulmonary tuberculosis, but died of tuberculous meningitis, and the sixth case died from transverse myelitis after a rather prolonged illness.

The mean plasma bicarbonate of 21.2 m.eq. per litre although the nighest in the group is still a low figure. It is thought from this that the shorter the duration of the disease the less will the plasma bicarbonate be depressed at death.

However, the conclusion that the plasma bicarbonate level is generally below normal at death agrees with both Whitney's and Hansen's findings.

A composite graph has been prepared from all the cases in which the plasma bicarbonate was estimated, showing the average of the readings on the various days before death (Figure 10).

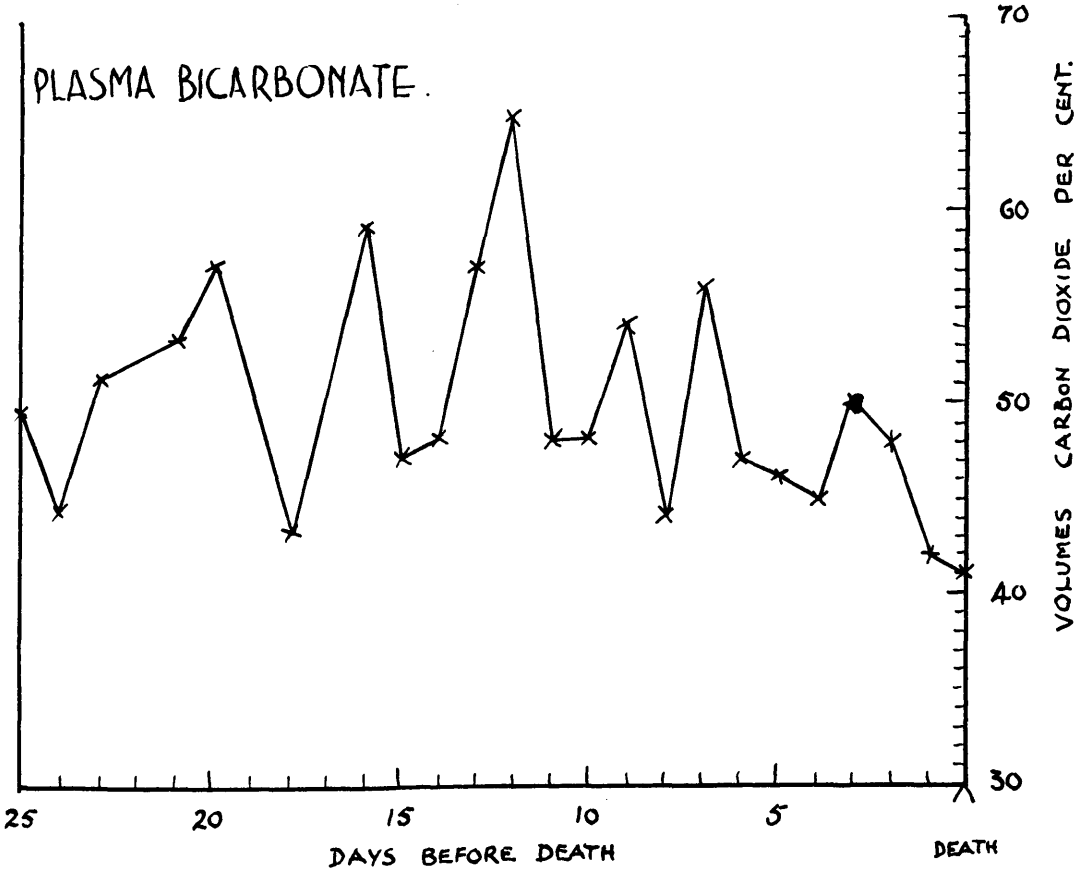


Figure 10.

The largest number of determinations were performed in the five days before death, and so the mean readings tend to give a more accurate picture of the changes in this period.

Elsewhere in the graph the points were plotted from the mean of fewer determinations and so tend to fluctuate.

It will be seen that there tends to be a steady although not a marked fall in plasma bicarbonate as death approaches. The fall seems to be more constant from about the third day before death.

b. Haemoglobin : Oxygen Saturation of the Blood.

In order to arrive at the actual oxygen saturation of a sample of blood, the haemoglobin content was first determined. A Sahli instrument newly calibrated to measure 14 g. haemoglobin at 100 per cent. was used throughout the work. 14 g. haemoglobin will carry 20.2 vols. oxygen per cent. (Haldane, 1920) and so the potential oxygen capacity of a sample of blood may be arrived at.

Haldane's gas analysis apparatus was used to determine the oxygen unsaturation of a sample of blood, and so by subtraction from the potential oxygen capacity the actual oxygen saturation was found.

Composite graphs (Figures 11 & 12) show the means of all the cases for haemoglobin and oxygen saturation on the various days before death.

As regards haemoglobin, it will be seen that the concentration steadily falls as death approaches, except in

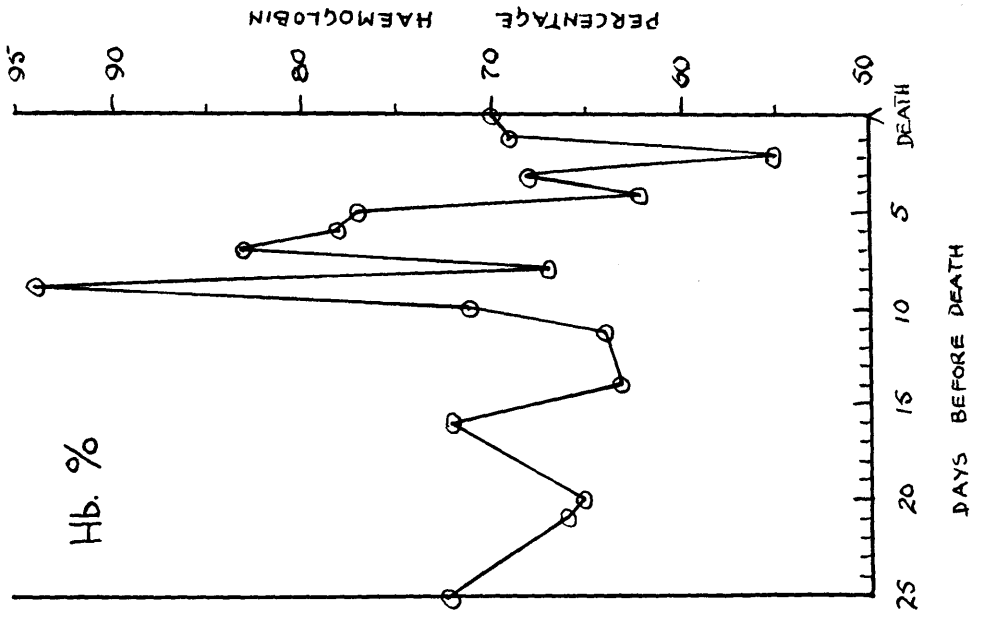


Figure 12.

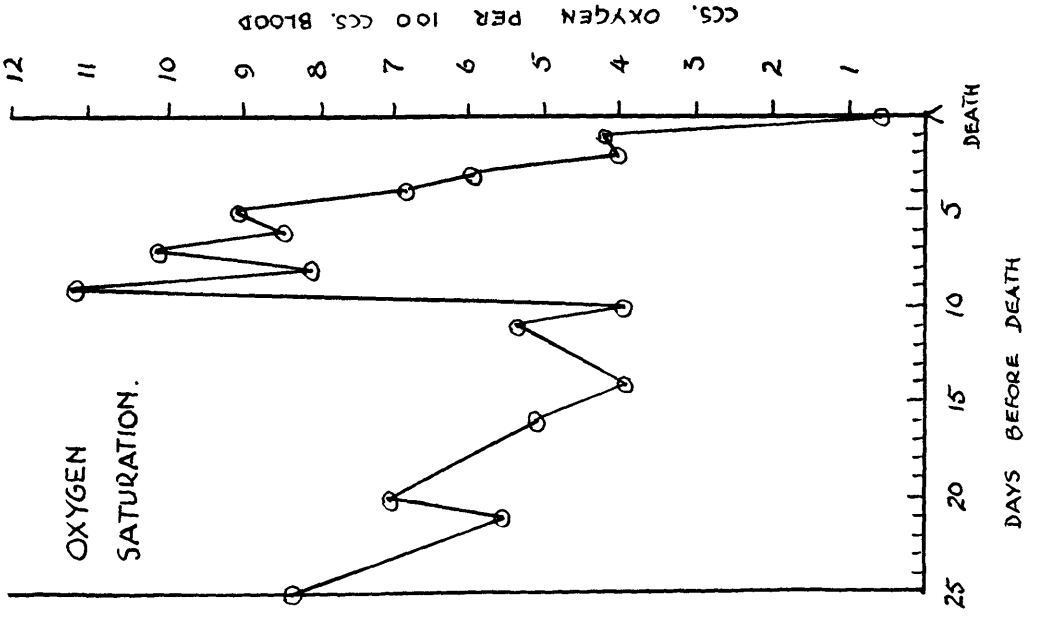


Figure 11.

the estimations done 24 hours before death, and immediately after death, when there is a sudden rise of about 15 per cent. There is little doubt that this terminal rise is due to haemo-concentration, which also corresponds with the period when the dying patient usually becomes comatose or semi-comatose, is collapsed and receives little fluid.

Hansen does not record haemoglobin findings in his series but observes that the finding of very high values for oxygen capacity at death undoubtedly signifies a considerable haemo-concentration. Hansen also noted that haemo-concentration might be simulated by intra-cardiac sedimentation of erythrocytes post-mortally. Samples may be withdrawn which are particularly rich or poor in erythrocytes depending on the position of the needle tip in the heart chamber.

It is the author's experience that this can certainly occur, but by withdrawing the blood within 10 minutes of death any great change can be avoided. It can also be seen from Figure 12 that sedimentation of erythrocytes is not the whole answer, since the reading at 24 hours before death is also high, yet these blood samples were taken by venepuncture.

The oxygen content of venous blood is not an accurate guide to the corresponding oxygen content of arterial blood, but if certain precautions are taken and conditions are standardised between patient and patient, general conclusions

may be drawn from the venous oxygen saturation.

Meakins & Davies (1920) showed that the relation between oxygen saturation of arterial and venous blood may vary 50-fold through the influence of external temperature.

Figure 13 sets out some of their findings showing the variations in venous oxygen saturation when the temperature of the arm is varied.

It will be seen that by immersing the arm in a water bath at a temperature of 45° C. for 10 minutes, the oxygen saturation of venous blood closely approximates to that of arterial blood.

Condition of Arm at Time of Experiment	Oxygen saturation of venous blood %.	Remarks as to colour of skin of arm
Normal conditions	56.4	Normal
Exposed to cool atmosphere	34.9	Faint blueness
Exposed to cold atmosphere	0.0	Very blue
Arm immersed in water bath at 45°C. for 10 minutes	94.2	Very pink
Arm immersed in water bath at 45°C. for 20 minutes	94.2	Very pink

Figure 13.

In the author's series of cases, it was felt that the most convenient standard condition would be to have the arm kept under the bedclothes close to the side of the body for about 10 minutes prior to venesection.

Hansen also used venous blood and blood from the left ventricle in making his oxygen saturation determinations, and concluded that it made little difference whether venous or "cardiac" blood was used, the results being similar. He mentions that the oxygen values in his series should be accepted with reserve.

Peabody (1913) investigated the changes in the oxygen content of venous blood in various cases of pneumonia. He recognised that the oxygen content of venous blood may vary widely, but in health the average is usually around 10 ccs. per 100 ccs. blood with a variation between 9.23 and 15.02 ccs. per cent.

Peabody's series was of 10 fatal cases of pneumonia, and he observed the oxygen content of venous blood at varying intervals up to death, and in one case immediately after death. In all the cases, the fall in oxygen content was progressive, for example blood taken two hours, one hour and 30 minutes before death contained 4.68, 2.3 and 2.07 ccs. oxygen per cent., and a specimen taken five minutes after death contained no oxygen.

Reference to the composite graph (Figure 11) of oxygen saturation values in the present series shows that there is a fairly wide fluctuation except in the last two or three days before death, when the oxygen saturation tends consistently to fall. The values at death in blood withdrawn from the heart - presumably from the left ventricle - are always low, the mean being 0.6 ccs. per cent.

The conclusion is reached then, that as death approaches, the oxygen content of venous blood falls, and that this fall is marked during the last three days before death. In general it can be assumed that these figures are a reflection of the oxygen content of arterial blood, which also falls steadily as death approaches.

The bearing which this demonstrated anoxaemia has on the other blood substances estimated will be referred to under the appropriate headings in the following pages.

c. Serum Calcium.

When the present work was commenced, it was decided to study the behaviour of the serum calcium in dying patients.

Nine patients were studied and 19 calcium determinations were made, the results being recorded as a composite graph in Figure 14.

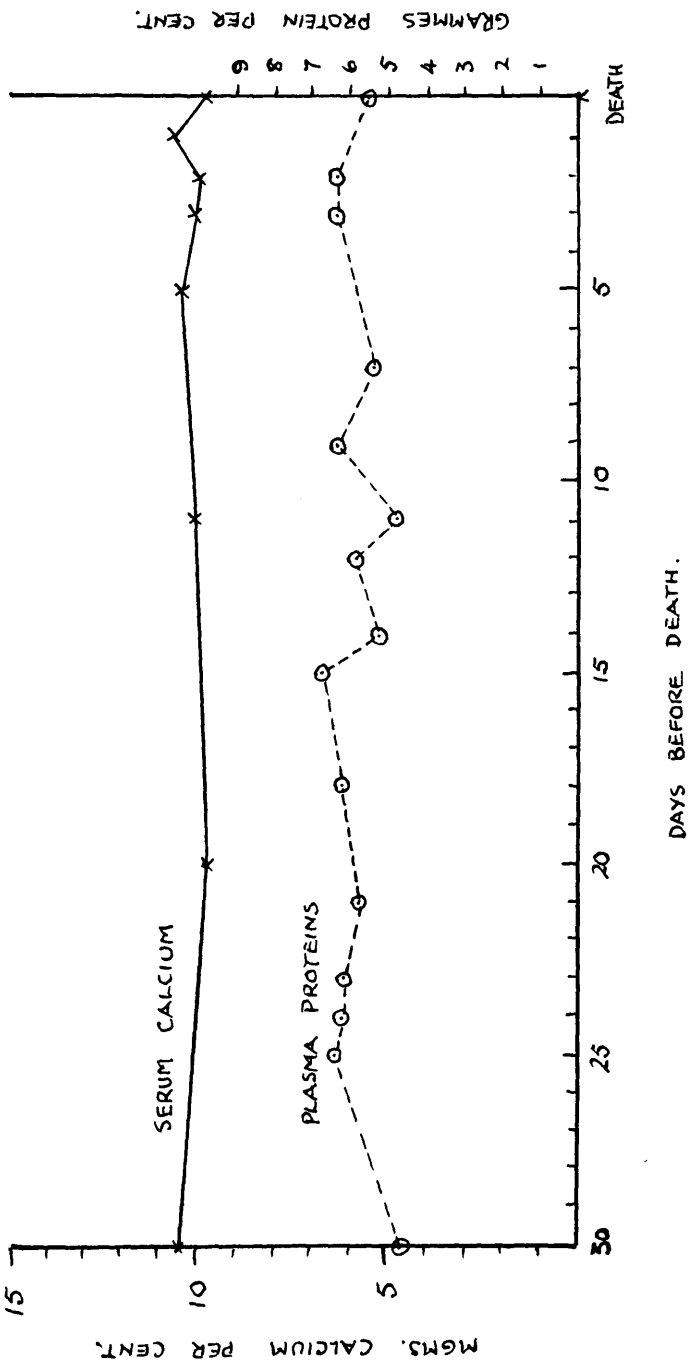

GRAMMES PROTEIN PER CENT.
9
8
7
6
5
4
3
2
1
DEATH
5
10
15
20
25
30
DAYS BEFORE DEATH.
MGMS. CALCIUM PER CENT.
15
10
5
SERUM CALCIUM
PLASMA PROTEINS

Figure 14.

It will be seen that there is no significant variation in serum calcium levels from the normal range of 9 to 11.5 mgms. per cent. (Hawk, Oser & Summerson, 1947), and the mean value at death was 9.8 mgms. per cent.

Hansen did not include the serum calcium in his study, and no other relevant reference to the subject appears in the literature.

It is known that the calcium content of the blood falls in chronic nephritis. Graham & Morris state that almost the total fall in the fixed base of serum is restricted to sodium and calcium in this disease. Stewart & Dunlop state that an acidosis causes at first an increase in the calcium of the blood, but that if the acidosis continues, increased excretion of calcium may lead to an ultimate lowering of the blood calcium.

It seems that the acidosis in the agonal state is not prolonged enough to cause much alteration in the level of serum calcium.

It was not considered worthwhile to continue the study of serum calcium in the remaining cases of the series and it was concluded that no significant alteration in the serum calcium occurs in the agonal or pre-agonal state.

d. Plasma Proteins.

Twenty-three estimations of total plasma proteins were made in eight patients. The results are shown by means of a composite graph (Figure 14).

The gravimetric method of estimating the plasma proteins was used (Phillips, Van Slyke, Dole, Emerson, Hamilton & Archibald, 1943). This method was found to give accurate results by Dimson & McMartin (1946) in the course of their work on blood analysis in Pamaquin haemoglobinuria.

The average figures in the present series of cases do not reveal any marked change in the level of plasma protein at death or in the preceding days.

The normal range of total plasma proteins is stated variously to be 6.2 to 8.0 gm. per 100 ccs. (Moore & Van Slyke, 1930), 6.1 to 9.6 gm. per 100 ccs. (Hawk, Oser & Summerson, 1947) and 5.8 to 8.6 gm. per 100 ccs. (Martindale, 1943).

The general levels for the series of cases studied tend to be towards the lower limit of normality, or in some cases below normal. The mean figure for plasma proteins at death in the present series is 5.44 g. per 100 ccs.

A long drawn out, debilitating illness might be expected to lower the plasma proteins gradually. Cuthbertson (1948) lists the causes of protein depletion and includes loss due to infection and loss due to disuse or reflex

atrophy (of muscle tissue), both of which seem applicable to the majority of patients studied in the present series.

The findings in Case No. 8 may be taken as an example. The patient was admitted to hospital on 20.4.1947 with transverse myelitis which never recovered. His condition gradually deteriorated and he developed extensive bedsores, chronic urinary infection and latterly oedema.

The plasma proteins on 9.7.1947 were 4.6 grammes per cent., and one month later on 8.8.1947 when he died they were 3.9 grammes per cent.

Hansen found normal and low values with almost equal frequency in blood taken at death or shortly before. He thought that several of his normal values should have been lower, and had been masked by haemo-concentration.

His conclusion that an agonal decrease in plasma proteins is rather common is supported by the findings in the author's series.

No sudden change in plasma protein values has been demonstrated, and it is thought reasonable that the generally low level is due to the negative nitrogen balance usually found in patients suffering from a debilitating illness and infection.

e. Blood Urea.

The question of protein metabolism in the dying would require a complete study in itself and it is not the intention in the present thesis to undertake this task.

The blood urea, however, was estimated in order to find out if any constant changes in its level occurred at death and in the days preceding, and to correlate any changes with those of other substances.

Stewart & Dunlop (1930) advise that the blood urea should be the substance of choice for estimation when derangement of the blood non protein nitrogen is expected. It is quantitatively the most important, and in disease shows the widest range of variation.

The normal blood urea figure is 20 - 40 mgms. per 100 ml. of whole blood (Martindale, 1943) and the mean figure at death in the present series was 87 mgms. per 100 ml.

As shown in Figure 15 the tendency was for the blood urea concentration to rise gradually as death approached, especially during the last ten days.

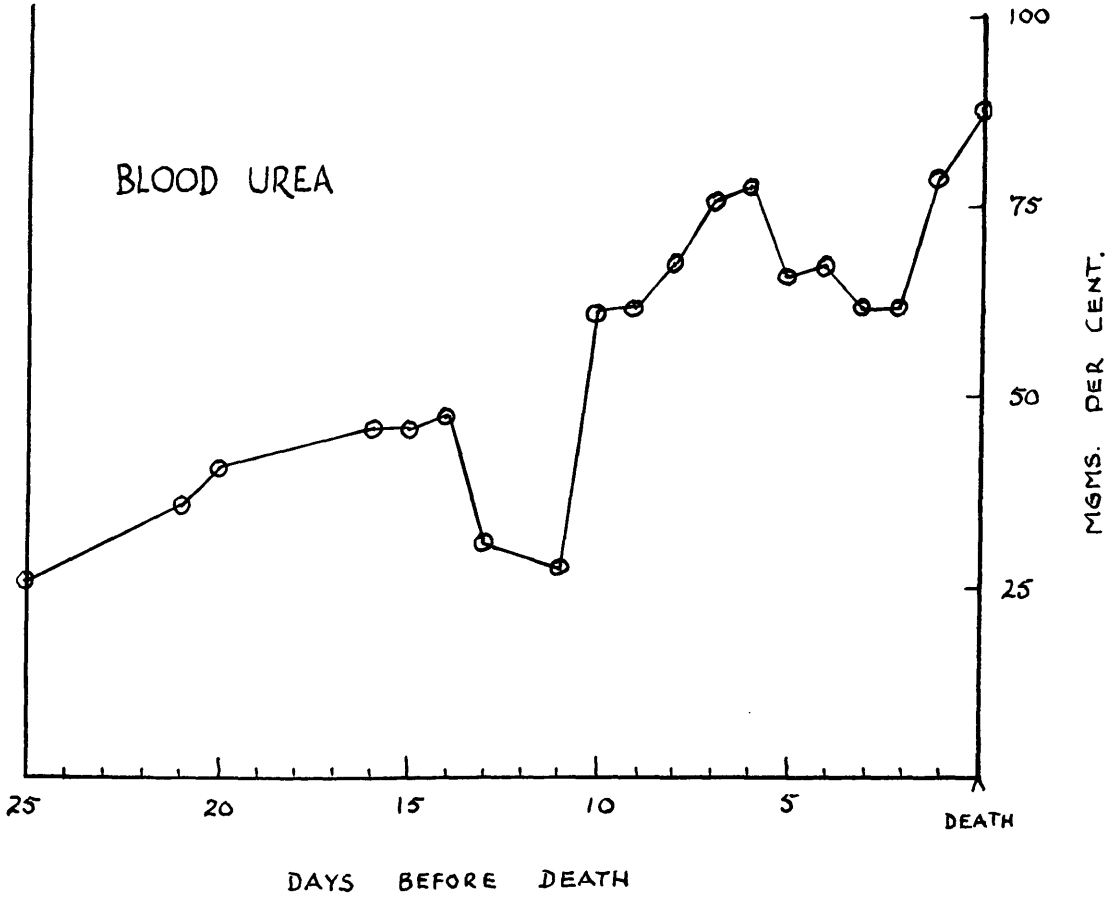

BLOOD UREA
100
75
50
25
MGMS. PER CENT.
25
20
15
10
5
DEATH
DAYS BEFORE DEATH

Figure 15.

Hansen also concluded that agonal uraemia is very common. The mean blood urea for the cases in his series was 76.9 mgms. per cent., which corresponds fairly closely to that of the author's series, and both agree with those of Whitney, who also found an agonal increase in blood urea.

To account for this agonal azotaemia, Whitney puts forward the view that the rise in urea is related to tissue breakdown, and secondly that pre-terminal reduction in kidney function further contributes to the development and maintenance of the azotaemia.

Baldwin (1947) writes: "For some time before death ensues there is a small but fairly constant daily excretion of nitrogen, the magnitude of which may be taken as an index to the amount of protein being broken down in the body. Death itself is heralded by a sudden extreme rise in the rate of nitrogenous excretion known as the "pre-mortal" rise, and this begins when the available carbohydrate and fat reserves of the tissues have been exhausted, and the organism is left with only its tissue proteins as a source of energy production, so that a large scale degradation of protein begins."

It is known that a high carbohydrate intake will depress endogenous protein katabolism (Bull, et al., 1949)

and so it can be assumed that in the terminal state, when little or no food is being taken that carbohydrate intake is low or sometimes nil and that consequently there is an increase in endogenous protein katabolism.

Cuthbertson (1948), discussing protein metabolism, says that for every degree Fahrenheit rise in temperature there is a 7 per cent. increase in the basal metabolism. When appetite fails during fever, the energy required comes from a utilisation of the tissues, indicated by an increased excretion of nitrogen. This situation is rather analogous to starvation, where some 13 per cent. of the energy expended comes from protein.

Borst (1948) in his paper on Protein Katabolism in Uraemia, found that infections appeared to have a deleterious effect on all patients with renal insufficiency; even in minor infections protein katabolism was definitely increased.

In one of his patients (Case 2) there was a rapid rise in the blood urea level, partly due to renal insufficiency, and partly due to a considerable formation of urea probably brought about by bronchopneumonia causing an extensive wastage of protein in the days immediately preceding death.

The great majority of dying patients take very little food during the several days before death, and in most there is pyrexia. It seems likely then that some at least of the

increase in blood urea concentration is due to increased tissue breakdown.

The azotaemia may also be partly accounted for by the mechanism of extra-renal uraemia which Zondek (1948) has extensively studied.

Extra-renal uraemia occurs in diseases not primarily involving the kidneys, and renal failure in such cases seems to be of a functional nature. A characteristic of extra-renal azotaemia, according to Zondek, is increased endogenous breakdown of protein which can be diagnosed by increase in the non-protein nitrogen in the blood and dissociation of the urea-sodium chloride excretion in the urine (large quantities of urea and small quantities of sodium chloride).

Extra-renal azotaemia occurs in various conditions such as burns, crushing, surgical shock and general infections such as Weil's disease, and Smith (1945) points out the constantly increased blood urea levels in severe haematemesis which is probably also a manifestation of this syndrome.

Although no evidence of gross renal failure was found in the present series as judged by the continued ability of the kidneys to form and excrete ammonia, it is thought that Zondek's extra-renal azotaemia occurred to some extent in the last 24 or even 48 hours before death.

In this period the patient was usually semi-comatose or even comatose, could not take fluid, and was in a state of collapse, with a weak, thready pulse. It will be shown in the section dealing with urine that in several cases the concentration of urinary ammonia fell in the specimen taken from the bladder at death, indicating a possible kidney dysfunction shortly before death.

It has been possible only to demonstrate the behaviour of the blood urea level in the pre-terminal state and to make tentative suggestions as to the cause of the changes found. Correlation with other blood and urine constituents will be made in a following chapter. To make any more dogmatic statement regarding protein metabolism at death would require much more extensive investigation than has been attempted here.

f. Plasma Bilirubin.

The plasma bilirubin was estimated in 35 cases of the series at various times in the pre-agonal state, and immediately after death. One Case, No. 27, was excluded because of jaundice caused by secondary carcinoma of the liver.

The estimation of plasma bilirubin was included because in the earlier cases studied it was noticed that the plasma at death was consistently icteric in colour.

Other yellow pigments such as carotinoids may appear in the plasma in cases of diabetes, in starvation, and in individuals who have been taking a diet very rich in vegetables (Stewart & Dunlop, 1930). In order to exclude these pigments the diazo method of measuring the plasma bilirubin was used.

Lups & Francke (1947) demonstrated the occurrence of a further yellow pigment different from bilirubin and carotinoids in the sera of healthy persons and icteric patients. Its presence was demonstrated in various diseases, but with no particular relationship to any one. Although the diazo method of estimating bilirubin does not differentiate this yellow pigment it was considered that the method would be accurate enough since the amounts of the pigment described by Lups & Francke are relatively small.

Vaughan & Hasslewood (1938) found that the level of plasma bilirubin in 100 healthy adults varied from 0.2 to 1.7 mgms. per 100 ccs, 93 per cent. of values being below 0.8 mgms. per 100 ccs. The mean value for the whole of their series was 0.539 mgm. per 100 ccs.

Whitby & Britton (1942) give the normal value of plasma bilirubin as 0.31 $\pm$ 0.03 mgm. per 100 ccs., while in the author's series the mean value of plasma bilirubin in 35 cases at death was 2.75 mgms. per 100 ccs. and the composite graph (Figure 16) shows that there was a steady rise in bilirubin concentration towards death.

Hansen did not study the plasma bilirubin in his series and no comparable reference to the subject appears in the literature.

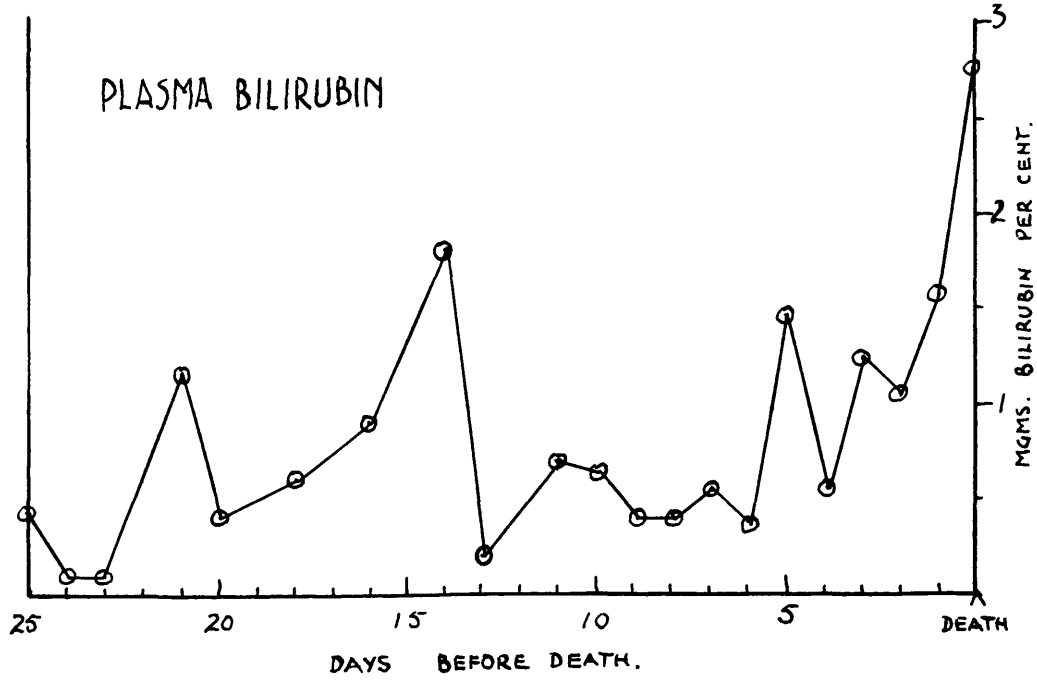


Figure 16.

Bilirubin is elaborated from the haemoglobin of the red blood corpuscles in the cells of the reticulo-endothelial system, mainly the Küpffer cells of the liver. The bile pigment formed in these cells is taken up by the polygonal cells lining the bile channels, and after slight modification is transferred to these channels (McNee, 1913).

Accumulation of bilirubin in the blood may arise in several ways:-

1. It may be caused by obstruction to the escape of bile from the fine bile channels, the pigment, which has passed through the polygonal cells, being re-absorbed into the blood stream.

2. It may be due to an inability of the polygonal cells to allow entrance of the pigment manufactured by the reticulo-endothelial cells, the pigment therefore passing direct into the hepatic vein.

3. There may be too great a synthesis of bilirubin, more than the polygonal cells could deal with, though functioning normally.

4. It may be due to a combination of obstruction and damage to the polygonal cells, or over-production of pigment.

According to Rich & Resnik (1926), the retention of bile pigment in the blood which occurs in practically every case of outspoken passive congestion of the liver is caused by two factors; impairment of the excretory function of the liver by anoxaemia and increased burden placed on the functionally impaired liver by the demand for the excretion of a larger amount of bile pigment than normally.

Kugel & Lichtman (1933) studied the cause of jaundice in various types of cardiac disease and concluded that anoxaemia of the liver cells alone did not produce clinical jaundice, but the incidence was increased after pulmonary infarction due to local haemolysis and resorption of bilirubin. Although Kugel & Lichtman were concerned only with clinical jaundice, they agree with Rich that anoxaemia of the liver cells does produce latent jaundice.

It is thought, therefore, that the hyperbilirubinaemia found in dying patients is likely to be due to anoxaemia, although not necessarily in conjunction with venous congestion. The oxygen supply of the liver is always rather precarious, and according to Trowell (1944) it is usually the first organ to show degeneration in conditions of chronic anoxia.

It has already been shown that anoxia is a feature of the agonal state, and damage to the liver cells is likely to occur with the consequent inability of the polygonal cells to deal with bilirubin normally produced. Thus there is a rise in plasma bilirubin in inverse ratio to the oxygen saturation of the blood.

It was not possible to distinguish the type of bilirubin formed, and modern tendency is to discount the interpretation of the direct, delayed and indirect van den Bergh reaction (Gray, 1947).

The question of haemolysis of red blood cells as a cause of the bilirubinaemia arose, especially since it is known that such haemolysis may occur in the Marchiafava-Micheli syndrome at night, when the pH of the blood tends to be at its lowest level (Hickey & Malley, 1948; Marks, 1949).

Hendry (1947) showed that haemolysis of red blood cells in vitro is accelerated if the pH of blood is lowered, and retarded if raised, concluding that the fragility of red blood cells depends on the pH of the blood.

In the present series of cases, no evidence of haemolysis could be found as judged by the absence of increased urobilin excretion in the urine on routine side-room testing.

None of the patients studied showed clinical jaundice. It is concluded, then, that progressive anoxia in the pre-agonal period causes liver dysfunction sufficient to produce a gradual increase in plasma bilirubin to levels above those which are generally accepted to be the upper limit of normal.

g. Plasma and Urinary Chlorides.

It has been thought best to present the plasma and urinary chloride results together although the other urinary findings will be left until the end of the chapter.

The plasma chloride, estimated as sodium chloride, was recorded in 43 cases at death and the mean reading found

was 571 mgms. per 100 ccs. The plasma chloride levels are depicted in the composite graph in Figure 17.

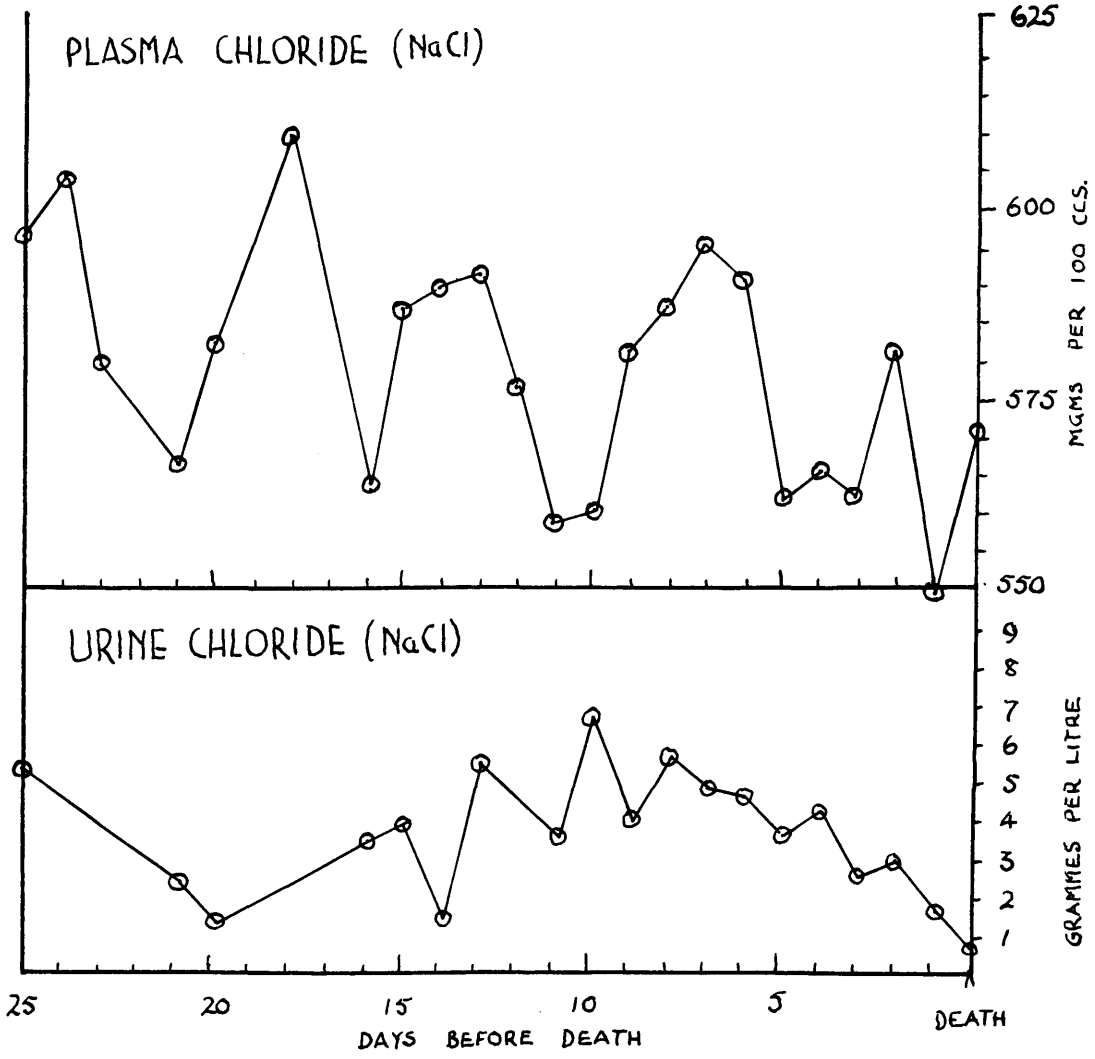


Figure 17.

The urinary chlorides were estimated in 24 patients, the results being expressed as grammes of sodium chloride per litre, and where possible, 24 hour collections of urine were

examined. As explained previously, it was sometimes impossible to obtain accurate 24 hour collections due to incontinence, in which case individual specimens were used. In all cases, the urine withdrawn from the bladder at death was an individual specimen, and the chloride concentration was expressed as grammes per litre.

The mean level of urinary sodium chloride in the 24 cases at death was 0.5 g. per litre, and the average of the other estimations on the days prior to death is shown in Figure 17.

While it is difficult to draw any conclusive opinion about the plasma chlorides, it will be seen that there is a very definite diminution of urinary chloride as death approaches. There would seem to be an approximate relation between the two, both tending to fall.

The normal range of plasma sodium chloride in health is given as 560 - 650 mgms. per 100 ccs. plasma by Van Slyke & Sendroy (1923) and 560 - 620 mgms. per 100 ccs. by Martindale (1943). The general level of plasma chlorides in the present series tends to be rather low, especially during the last five days of life, the lowest mean value of 549 mgms. per 100 ccs. being recorded 24 hours before death.

The rise to 571 mgms. per 100 ccs. at death is thought to be due to dehydration and possibly kidney dysfunction occurring during the 24 hours before death.

Dehydration alone accounted for the increase in chlorides, plasma proteins and lactic acid in 27 children suffering from diarrhoea and vomiting following mastoiditis (Hartmann, 1928; Aldridge, 1941).

Aldridge (1941) showed that there was a steady rise of plasma chlorides in the pre-agonal period of infants suffering from gastro-enteritis with dehydration, and values of over 900 mgms. per 100 ccs. were recorded in a few cases.

It is the author's impression that a steep fall in plasma chloride at death was masked by dehydration, because in several cases in the series where death was relatively quick and dehydration minimal, very low values were recorded:

Case 15, who died of congestive cardiac failure 2 days after admission had a plasma chloride of 522 mgms. per 100 ccs. at death (Figure 18).

Case 19 was a patient with severe tuberculosis who died quickly 5 days after admission. The plasma chloride was 512 mgms. per 100 ccs. at death, having fallen from a level of 556 mgms. per 100 ccs. three days previously (Figure 19).

Another example of the steep fall of plasma chlorides at death in a patient who died relatively quickly is shown by Case 27. This patient, although he had carcinoma of a bronchus, was in quite good general condition up to a few days before death. The speed of death was due to rapid growth

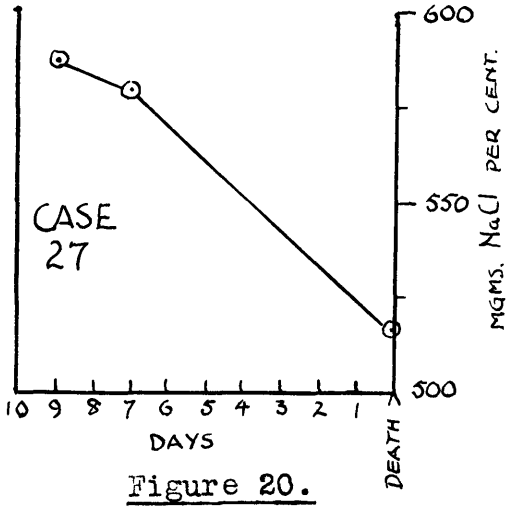


Figure 20.

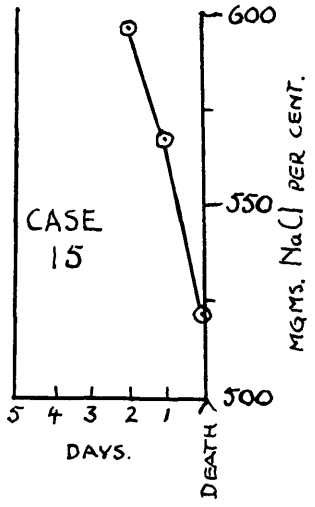


Figure 18.

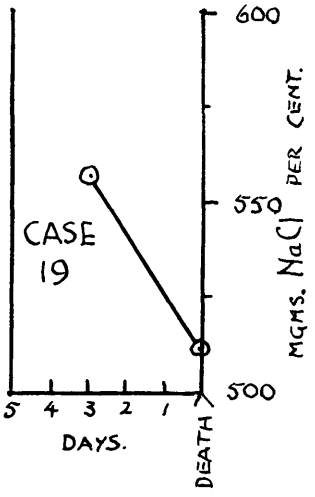


Figure 19.

of secondaries in the brain. The plasma chloride fell to 519 mgms. per 100 ccs. at death, having been previously within normal limits (Figure 20).

The mean agonal level of plasma chloride in Hansen's series was 584.4 mgms. per 100 ccs. with a range of 474 to 705 mgms. per 100 ccs. This corresponds closely to the figure of 571 in the author's series.

Hansen concluded that an agonal decrease in plasma chloride is more common than an increase, but is rather vague in his explanation of the change, which he thinks might possibly be due to a terminal pneumonia or inability of the kidneys to retain chloride - in analogy with the increased chloride excretion often seen in advanced nephritis.

In the present series, the low plasma chloride levels at death tend to be even lower than in Hansen's, but it is the author's opinion that terminal pneumonia of pyogenic origin is not the reason, and in any case it is rather a hypothetical condition. Nor does it appear to be due to increased excretion of chloride, since the results show that the chloride concentration of the urine steadily falls towards death.

It is thought that the shift of Cl^- ions from plasma to red corpuscles which occurs in acidosis is sufficient to account for the fall in plasma chloride. It is also

possible that there is an element of adreno-cortical failure (Cameron & Carmichael, 1946) especially in asthenic and cachectic patients, which, in analogy with Addison's disease, may cause hypochloraemia.

The conclusion drawn from the present findings is that the plasma chlorides tend to be lower than normal, and sometimes very low in the agonal and pre-agonal period. There is a steady diminution in the chloride concentration of the urine as death approaches.

h. Plasma Phosphorus and Blood Lactate.

The plasma phosphorus and blood lactate will be considered together in this chapter because the two substances are inter-related in their behaviour when there is a state of anoxaemia. The latter condition has been shown to be frequent in the days preceding death.

The plasma phosphorus was estimated at various times in 48 cases of the series. The mean value found at death was 5.6 mgms. per cent., and the mean level in the days preceding death is shown in the composite graph (Figure 21).

The blood lactate was estimated in 26 cases of the series at various times during life and at death. The mean level at death was found to be 65 mgms. per cent., and the levels preceding death are shown in the composite graph (Figure 22).

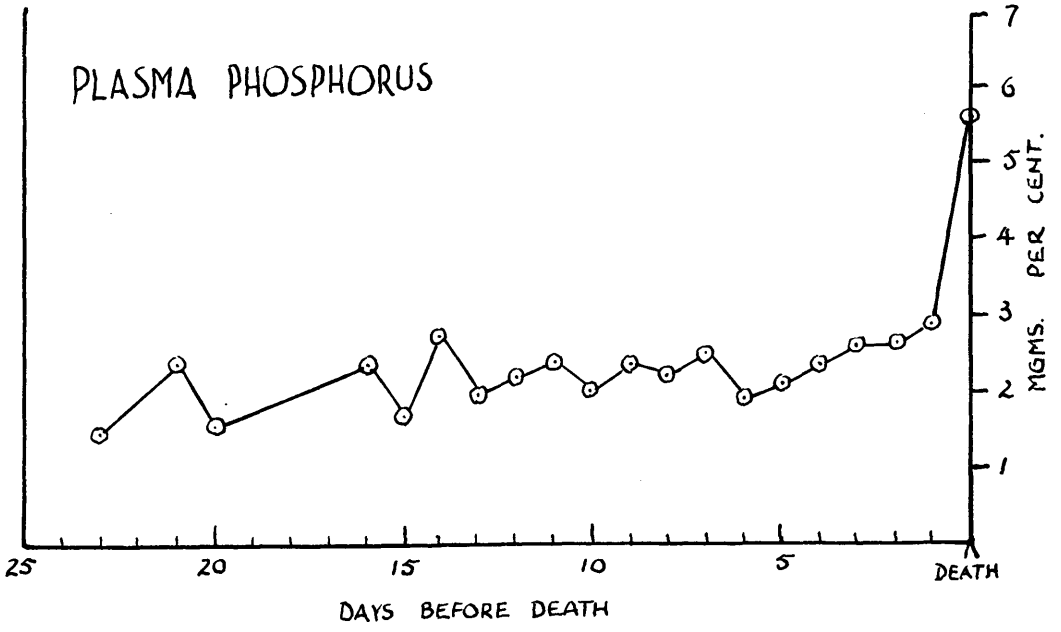

PLASMA PHOSPHORUS
7
6
5
4
3
2
1
MGMS. PER CENT.
25
20
15
10
5
DEATH
DAYS BEFORE DEATH

Figure 21.

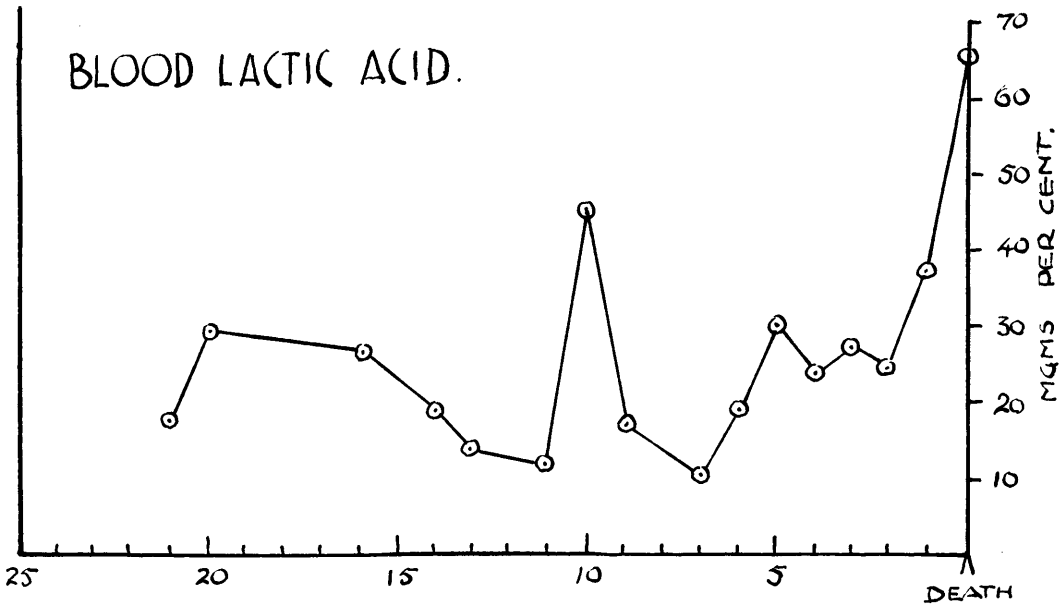

BLOOD LACTIC ACID.
70
60
50
40
30
20
10
MGMS PER CENT.
25
20
15
10
5
DEATH

Figure 22.

The normal range of values for plasma phosphorus is given as 2 - 4 mgms. per cent. for adults and 4 - 6 mgms. per cent. for children (Martindale, 1943).

For blood lactate, the normal range of values is given by Hawk, Oser & Summerson (1947) as 5 - 20 mgms. per cent., but there seems to be a fairly wide divergence of views on what should be regarded as the average normal level.

Jervell (1928) in his own experiments found 27.38 mgms. per cent. to be the mean normal level, and the table below (Figure 23), adapted from Jervell, shows the figures of other authors.

Author	Year	Normal Values of Lactic Acid in mgms.%.
Berlinblau	1888	8
Ryffel	1909	12.5
Fries	1911	9.63
Lichtwitz	1914	20 - 40
Clausen	1922	15 - 32
Himwich, Loebel, Barr, Green	1923-4	10 - 25
Hill & co-workers	1924	10 - 20
Long	1924	10 - 15
Barcroft	1925	12 - 24
Mendel, Engel, Goldschneider	1925	15 - 16
Collazo, Lewicki	1925	15.9
Schenk	1925	17 (6 - 22)
Bohelmann	1927	17.3 (15.2 - 21.3)

Figure 23.

It will be seen that the mean phosphorus values in the pre-terminal state remain within the normal range, and that the level seems to rise only in the last 24 hours of life.

The highest value found was in Case 21, where the level of plasma phosphorus was 18.2 mgms. per cent. at death, having been only 3.7 mgms. per cent. 48 hours previously. This patient died of advanced pulmonary tuberculosis, and unfortunately corresponding blood lactate estimations were not done in this case.

An interesting effect of the administration of oxygen on the phosphorus and lactate levels is shown in Case 34. This patient had acute bronchopneumonic tuberculosis aggravated by an abortion. She was extremely cyanosed and dyspnoeic for several days prior to death, and oxygen was administered by BLB mask on the 5th and 6th days before death.

The effect obtained is recorded in graphic form in Figure 24, and it will be seen that the oxygen saturation of the venous blood was improved, while the blood lactate fell markedly and the phosphorus fell to a lesser extent. On discontinuing oxygen therapy, the phosphorus and lactate values rose, and the oxygen saturation of the venous blood returned to nil.

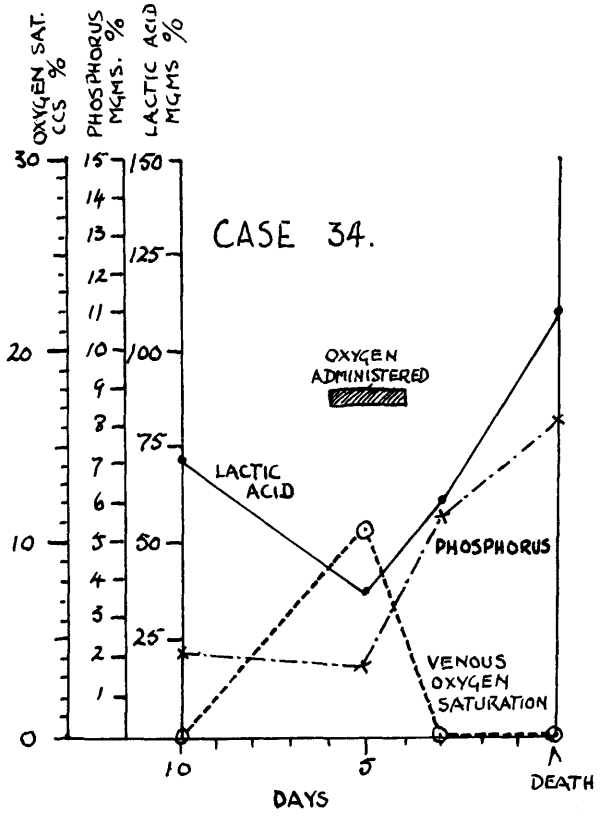

OXYGEN SAT. CCS %
PHOSPHORUS MGMS. %
LACTIC ACID MGMS %
CASE 34.
OXYGEN ADMINISTERED
LACTIC ACID
PHOSPHORUS
VENOUS OXYGEN SATURATION
DEATH
DAYS
30
20
10
0
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
150
125
100
75
50
25
10
5

Figure 24.

Hansen (1948), who of course made his estimations only at death, found a mean agonal value for serum phosphorus of 4.6 mgms. per cent. The highest figure for his series was 9.2 mgms. per cent. These values compare with 5.6 and 18.2 mgms. per cent. respectively in the author's series.

Hansen concluded that the increase in serum phosphorus is a common agonal phenomenon.

Jervell (1928) investigated the behaviour of plasma inorganic phosphorus in persons subjected to exercise. He found a definite rise in the plasma phosphorus along with a rise in lactic acid and a decrease in the alkali reserve brought about by exercise.

The increase in the quantity of phosphorus was materially less than the equivalent quantity of lactic acid. An example from one of his cases (No. 13) is illustrative:- There was an increase of lactic acid from 21 mgms. per cent. to 45.5 mgms. per cent. and a fall in alkali reserve, along with an increase of plasma inorganic phosphorus from 2.99 mgms. per cent. to 4.0 mgms. per cent. In other words, as Jervell puts it, there is a breakdown of hexose phosphate during the anaerobic phase in severe exercise with formation of equivalent quantities of lactic acid and phosphoric acid.

As regards the blood lactate values in the author's series, it will be seen from the shape of the graph in Figure 22 that there is a significantly steep rise in the

last 48 hours before death. The values in the days preceding this period range between 10 and 30 mgms. per cent. The spike on the graph at the 10th day is due to an abnormally high value of 72 mgms. per cent. in Case 34, the patient being severely dyspnoeic at the time.

Study of the changes in phosphorus and lactate show that there is a sudden increase in the blood levels of both these substances shortly before death, and comparison with the graph of venous oxygen saturation would indicate that this is due to tissue anoxia. Presumably the metabolism reverts partly to the anaerobic type.

The figures for blood lactate quoted by Hansen are interesting. He found that the plasma lactic acid was increased in all samples taken pre- and post-mortally, and in many cases the values were so high that they rank with the highest ever reported in the literature. Hansen thinks that this finding has to be taken as being peculiarly characteristic of the agonal state.

The mean control value in his series was 12.6 mgms. per cent. with a range of 7.2 to 22.5 mgms. per cent. the subjects having rested for 30 minutes.

The mean value for all pre- and post-mortal samples was 98.1 mgms. per cent., but the mean value in the seven cases in which the blood was examined shortly before death

was 46.8 mgms. per cent., while the mean value in the remainder of the cases in which blood was taken after death was 109.8 mgms. per cent.

In the author's series, the mean agonal value of blood lactate is 65 mgms. per cent. which although a high value is much lower than that found by Hansen. Also, the mean blood lactate recorded within 24 hours of death in the author's series of cases was 37 mgms. per cent. and in the days prior to this the values fluctuated between 20 and 30 mgms. per cent.

The results now recorded substantiate Hansen's statement that the level of lactic acid in the blood rises to very high values at death in all cases. Further, it can be said that the rise in blood lactic acid tends to occur about 48 hours before death and is progressive.

A word remains to be said regarding the cause of the increased levels of blood phosphorus and lactate at death. Hansen does not give any explanation of the rise of blood phosphorus, but considers that the high lactate levels may be partly due to cardiac insufficiency which must be assumed to exist for some time before cessation of cardiac activity.

It has been shown that the blood lactate does tend to rise in congestive cardiac failure (Jervell, 1928; Hawk,

Oser & Summerson, 1947) but the primary cause of the lacto-acidaemia is anoxia which is secondary to cardiac failure. This is also the explanation of the increased blood lactate values found in peripheral stasis, and after severe exercise (Lundsgaard & Möller, 1923).

Hansen discounts the theory that liver function is so depressed that it prevents circulating lactic acid from being converted into glycogen, since his cases with icterus showed lactic acid levels only very slightly above the mean for all the patients.

Although the author has also shown that formation of urea by the liver is not impaired even up to the time of death, it is likely that there must be some impairment of glycogen formation, since Cori & Cori have shown that circulating lactic acid requires oxygen in order to convert it to pyruvic acid and through the stages of phosphorylation to liver glycogen.

It seems clear, however, that the primary cause of the rise in blood phosphorus and lactate is due to the process of anaerobic cellular metabolism. This also occurs during strenuous exertion in a healthy subject, in congestive cardiac failure, as well as in the few hours preceding death.

The actual biochemical process by which phosphorus and lactic acid are freed in the tissue fluids and blood has been mentioned in the chapter on Theory, and will also be considered later in the discussion.

The Urine.

i. Hydrogen Ion Concentration.

A total of 150 estimations of the pH of urine were performed in 45 cases of the series.

The mean pH value of the urine catheterised from the bladder immediately after death was 5.08, with a range of 4.6 to 5.8.

The graph (Figure 25) shows the composite curve obtained by plotting the mean values for the various days before death. It will be seen that up to about 5 or 6 days before death the reaction of the urine fluctuates in the normal manner and that nearer death it becomes fixed at a more acid level and steadily falls until it reaches pH 5.08 at death.

In health, the pH of mixed specimens of urine over 24 hours is approximately 6 (Thorpe, 1940; Martindale, 1943) although there is a fairly wide fluctuation depending on the type of diet taken. In general, carniverous animals and men on a mixed diet pass an acid urine.

Devising their own colorimetric pH standards, Henderson & Palmer (1913) found that normal urine usually ranged between pH 4.82 and pH 7.45, the mean value being 6.0.

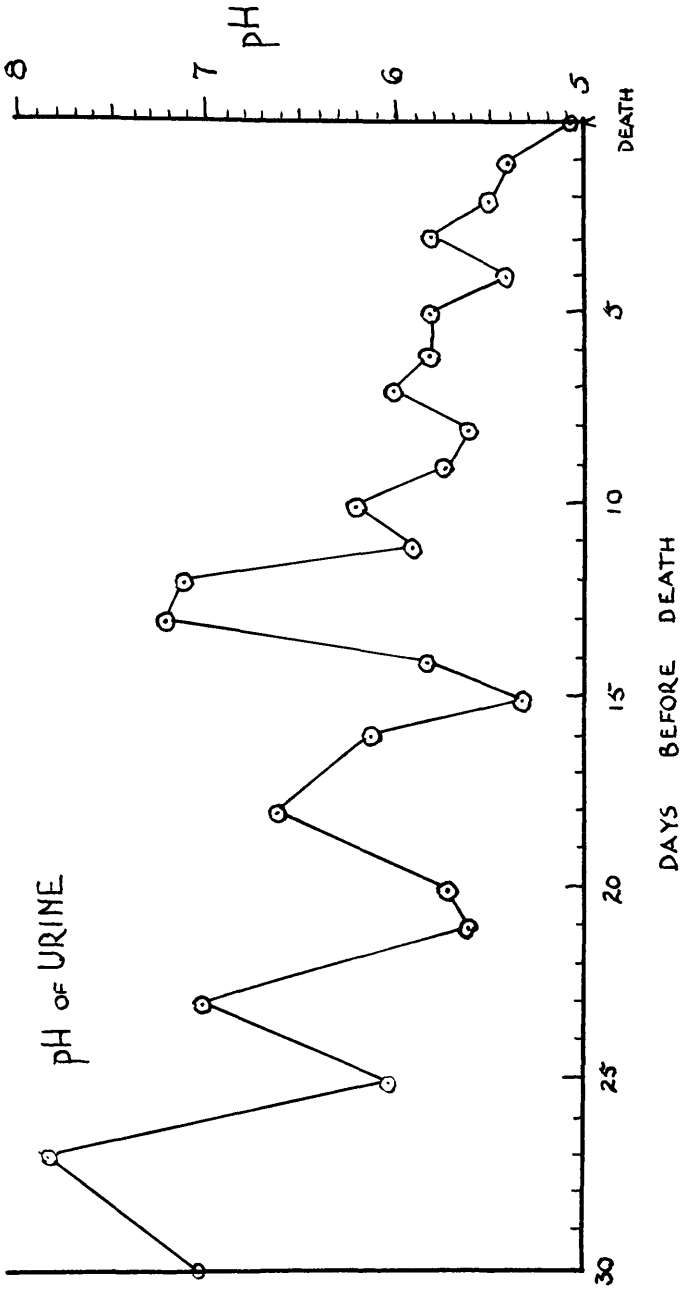


Figure 25.

The acidity of the urine may be increased after strenuous muscular exercise, by ingestion of ammonium salts of strong acids, e.g. Ammonium chloride, or by pathological conditions promoting acidosis, notably diabetic coma (Thorpe, 1940).

Morris & MacRae (1930) showed that after ingestion of ammonium chloride the urine became very much more acid, and that the ammonia and titratable acidity were increased.

McCance & von Finck (1947) say that pH 4.9 is about the limit of acidity at any age.

It is clear then that in the pre-terminal state the pH of the urine tends to become fixed at a low level, which continues to fall steadily up to the time of death.

j. Titratable Acidity and Ammonia Content of Urine.

An adult on a mixed diet normally excretes the equivalent of 33 - 60 N/10 acid per 100 ccs. urine over the day (Thorpe, 1940). Part of this is in the form of acid which can be titrated against sodium hydroxide, 13 - 27 ccs. N/10 per 100 ccs., and part in the form of ammonium salts, 20 - 33 ccs. N/10 per 100 ccs.

In severe diabetic acidosis a total of 6,000 ccs. N/10 acid per day may be eliminated - equivalent to about 400 ccs. N/10 acid per 100 ccs. of urine.

The titratable acidity and ammonia excretion in the urine was measured at various times before and at death in 37 cases of the present series. The results, for reasons given previously, are expressed as ccs. of N/10 per 100 ccs., and the mean curves are depicted in the graph in Figure 26.

The mean excretion of ammonia and titratable acidity as shown by measurement of the urine catheterised at death is 77.3 and 68.4 ccs. N/10 per 100 ccs., which gives a total acid secretion of 145.7 ccs. N/10 per 100 ccs. This is considerably higher than the normal range of 33 - 60

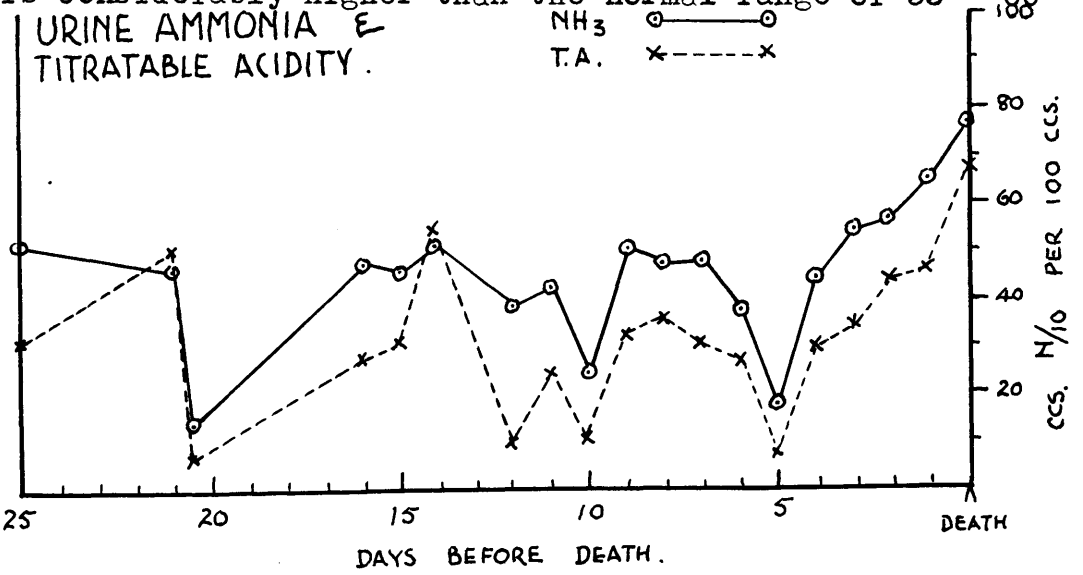


Figure 26.

ccs. N/10 per 100 ccs.

It will be seen that the levels of ammonia and titratable acidity begin to rise steadily from about the 5th day before death. Before this there is a wide fluctuation from day to day in the excretion of the two substances,

but tending generally to be a little above normal.

These urinary findings are therefore consistent with what one would expect in a moderate acidosis.

The ratio of acid to ammonia is also of interest. Palmer & Henderson (1915) found the average normal acid - ammonia ratio to be 0.785., but that in disease severely affecting the glomeruli of the kidneys, the ratio may rise to as much as 1.4.

Only in isolated estimations in the present series did the acid - ammonia ratio rise above unity, and then only slightly.

CHAPTER VIII.

DISCUSSION

The biochemical alterations in the blood and urine as death approaches have been depicted in the foregoing chapter, and it is now necessary to examine the results and attempt to explain them as far as possible from physiological principles.

It will be seen that the majority of constituents examined showed no great alteration from normal up to a few days before death, and even in the immediate pre-agonal period no dramatic changes occurred, although they were significant and fairly constant.

Taking the results as a whole, the general pattern seems to be that of a moderate acidosis. The low plasma bicarbonate and high lactic acid and phosphorus levels in the blood, and the low pH and high acid and ammonia content of the urine point definitely to this.

However, one is accustomed to expect a much more severe acidosis in diabetic coma, chronic nephritis or in gastro-enteritis of infants.

Since the blood pH was not estimated in the present investigation, it has not been possible to classify the precise type of acidosis present. Hansen (1948), on the other hand, was able to do this by using the diagram prepared by Peters & Van Slyke (1931) on which are plotted as logarithmic co-ordinates the values of plasma pH, bicarbonate and carbon dioxide tension.

The majority of his patients, 30, had a mixed type of acidosis, partly respiratory and partly metabolic, while five were classified as purely metabolic and three as respiratory. Hansen points out that this is an unusual type of acidosis to find and that Peters & Van Slyke discovered only 10 such cases out of 450 cases of non-agonal acidosis.

The interesting feature, however, is not the type of acidosis present at death, but the method of its development. This, Hansen did not study, for he only made one set of estimations on each patient, usually immediately after death, and in seven cases very shortly before.

From a study of the mean results depicted in the graphs in the previous chapter, the table below (Figure 27) has been prepared to show approximately the number of days

before death when a definite change in the trend of the estimated substance was found, either a fall or rise.

	Estimation	Number of Days before Death when Change in Trend of Values noted.
BLOOD	Plasma bicarbonate	3 - 5
	Venous oxygen saturation	2
	Plasma bilirubin	3
	Plasma chlorides	5
	Blood lactate	2
	Plasma phosphorus	1
	Blood urea	10
URINE	pH	3
	Chloride	3
	Ammonia & Titratable Acidity	3

Figure 27.

It can be seen that a change is generally obtained, except in the case of blood urea, about 2 to 4 days before death. A study of the case histories reveals also that at this period before death the character of the patients' respirations changes. Dyspnoea becomes more apparent, and the patient becomes drowsy and sometimes semi-comatose. The respiratory excursion does not seem to be full enough

to make good the oxygen lack which is obviously present, and fatigue of the muscles of respiration and of the respiratory centre supervenes. The respiratory derangement becomes progressively worse until death.

It would appear possible that anoxia, which can produce violent metabolic upsets in other conditions, might be responsible for the train of biochemical events in the pre-terminal state.

The work of Koehler, Behnemann, Benell & Loevenhart (1925) which has already been dealt with fully in a previous chapter may be briefly mentioned again as an illustration of the effects of anoxia. It will be recalled that these authors studied the response of pigs to anoxia, measuring the blood pH, total carbon dioxide, carbon dioxide tension and respiratory rate.

Two of their experiments have been reproduced graphically (Figures 28 & 29) and are self-explanatory.

It may also be recalled that the animals which were given a solution of sodium bicarbonate intravenously lived 2.5 times as long as the controls, and that this was explained by assuming that the vicious circle of acidosis induced by anoxia and thereby in turn causing impairment of oxygen utilisation was to some extent broken.

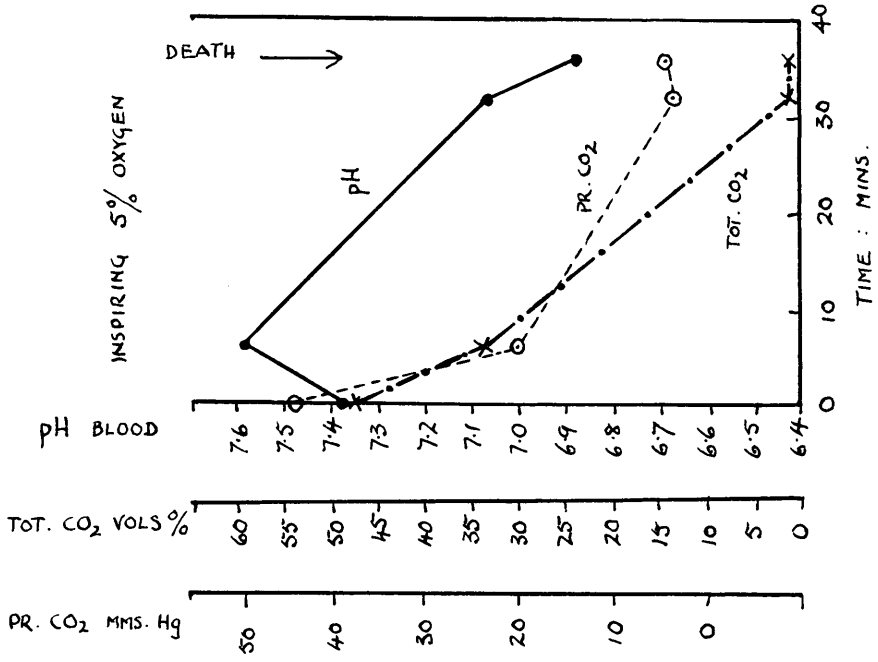


Figure 29.

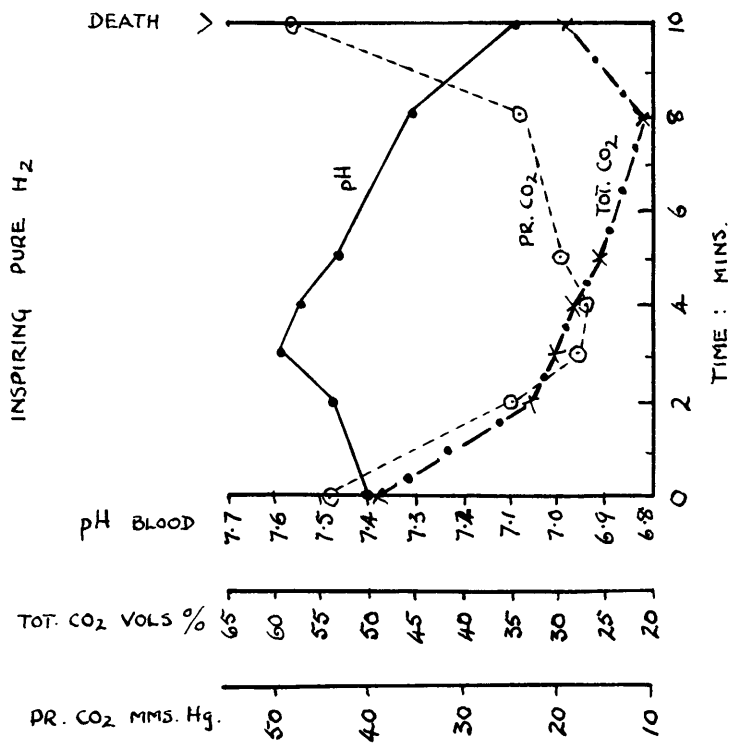


Figure 28.

In order to explain the crude biochemical findings of Koehler's experiments, and also of the present series of cases, it is necessary to consider certain work which has been done in the field of micro-biology.

Walter Kempner (1939) made some interesting observations concerning the rôle of oxygen tension in biological oxidations. It had been an unquestioned fact before this that cell respiration was entirely independent of variations in oxygen tension, and that it continued at its optimal rate as long as the smallest amount of oxygen was available (Warburg, 1908). But Kempner, experimenting on a wide range of cellular tissue found that under physiological conditions at 37° C., all nucleated uninjured blood cells, and a great number of young bacteria, showed a decisive dependence of their respiration on variations of oxygen tension.

Tubercle bacilli because of their relative resistance and slow growth were found suitable organisms to demonstrate oxygen consumption at various oxygen tensions over periods up to 36 hours, and the result of one of these experiments is shown graphically in Figure 30.

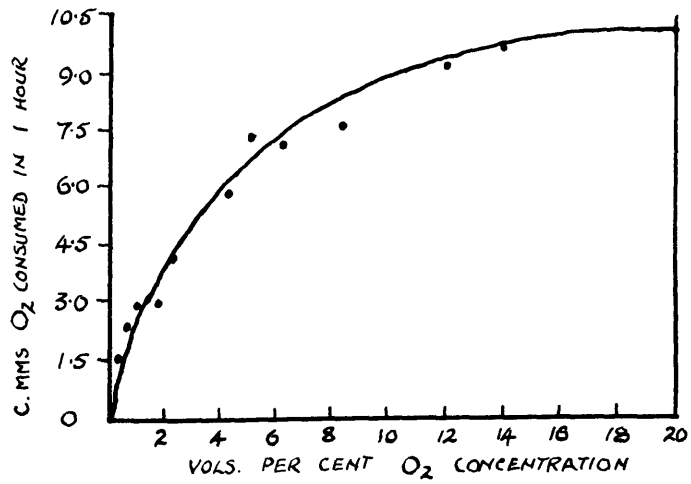


Figure 30.

Rate of respiration of 1 mgm. dry weight of Tubercle bacilli H37 at various oxygen concentrations, 37.8° C.

Pasteur (1879) had discovered that many cells form lactic acid in the absence of oxygen, and the Warburg - Meyerhof theory postulates that every decrease in respiration brings about a direct increase in the formation of lactic acid.

Most normal animal cells show respiration and no lactic acid formation when examined in air or in pure oxygen,

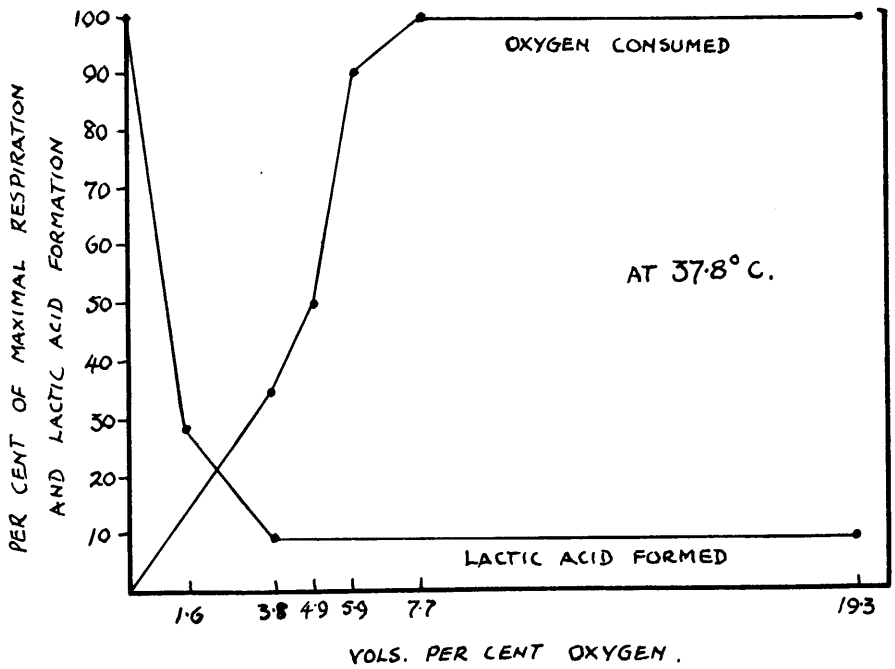


Figure 31.

but in the total absence of oxygen when respiration is zero, lactic acid is found in large amounts. The diagram (Figure 31) after Kempner (1937) illustrates the reciprocity of oxygen and lactic acid in cellular respiration. It will be noticed that the tissue can withstand a fair degree of oxygen lack

before respiration is impeded and lactic acid formed. Kempner, working with nucleated, uninjured red blood cells showed that at 4.9 vols. per cent. oxygen respiration was inhibited by 49 per cent. compared to that in air, but with no increase in lactic acid formation, and even when the respiration was inhibited up to 70 per cent. compared to that in air, the cells failed to react with any kind of lactic acid formation (Figure 31). At lower oxygen concentrations, however, lactic acid was formed in increasing amounts.

It is evident, therefore, that tissues, although they have a good resistance to a moderate degree of oxygen lack, will ultimately produce large amounts of lactic acid if the oxygen supply is reduced still further.

Severe anoxaemia has been a constant finding in the period immediately before death in the present series of cases, and was the direct cause of acidosis in Koehler's experimental pigs. The findings in Kempner's micro experiments could be applied to what is happening to the tissues of the human body shortly before death and also to those of the pig subject to anoxia.

The question arises: are the tissue cells of a person dying with some chronic, toxic disease (such as tuberculosis or carcinoma) normal? This point is raised because Kempner (1939) also found that cancer cells and injured tissue

cells (whether by cyanide, carbon monoxide, or various toxins leading to gradual death of the cell" behaved in a totally different way from normal tissue.

These abnormal cells formed large amounts of lactic acid under aerobic conditions, and the first sign of the dying-off of cells according to Kempner is injured respiration, so that large amounts of lactic acid appear even in air. In short, Kempner explains this phenomenon by a direct pathological change in the catalytic system of the cells whereby an irreversible change occurs in such a way that their capacity of spontaneous reaction with oxygen is lost once and for all.

That the tissue cells of patients dying of a chronic disease such as tuberculosis are injured is possible. They may respond to anoxia, at least to a degree in the same manner as Kempner's experimental damaged tissue, and their ability to respire normally may be altered.

It would be extremely difficult to prove that the respiratory change was irreversible, or if so at what point.

Not all deaths follow toxaemia such as is found in tuberculosis, and death following cerebral haemorrhage might be accompanied by very little.

Many cases are on record where persons have been revived by artificial respiration or cardiac massage. In

most cases of this kind the tissues of the body have been subjected to complete anoxia for varying intervals and yet have been revived to live again. One cannot postulate the theory of irreversible change here, although it must be said that most persons who require artificial respiration are otherwise healthy and have healthy tissue cells.

The reversibility of the biochemical changes in the blood and urine have been demonstrated in two cases of severe congestive cardiac failure who recovered (Cases A and B, Appendix). The temporary beneficial effect of oxygen on the raised blood lactic acid and plasma phosphorus has also been demonstrated in a case of tuberculous broncho-pneumonia (Case 34, Figure 24).

Kempner's experimental evidence that the respiratory function of damaged cells can be irreversibly impaired may still be a factor operating in the immediate pre-agonal phase of chronic infective disease. More than that cannot be said.

Anaerobic metabolism in the new-born infant has been studied by Wilson et al. (1948). They think it highly probable that the new-born human, as well as the new-born of other species makes use of an anaerobic mechanism in his foetal life which is lost soon after birth. This mechanism

reaches an end point in the carbohydrate breakdown short of carbon dioxide and water.

Wilson et al. found a lowered blood pH, lowered alkali reserve, increased blood lactic acid and increased urinary excretion of organic acids in new-born babies. They deduced that the metabolic acidosis is an indication of anaerobic metabolism, and of the production of an end product other than carbonic acid, such as lactic and pyruvic acids. This enables the infant to maintain life with a great economy of oxygen. Wilson's investigations show again how adaptable are the healthy human cells in response to anoxia and how they can withstand this abnormal environment for long periods without ill effect.

The behaviour of the plasma phosphorus in the pre-terminal state may now be considered further. Great fluctuations in the levels were not found except in isolated cases, and the mean value remained within normal limits up to 24 hours from death.

It is well known that the plasma phosphorus rises, sometimes to very high values, in chronic kidney diseases with impaired excretory function, and the possibility that the terminal rise of plasma phosphorus at death might be due to functional renal impairment must be considered.

Specific tests of renal function were not done in the author's cases, but on clinical evidence it has been

assumed that no organic kidney disease was present. This was confirmed in the five cases on which autopsy was carried out.

It has been clearly shown that azotaemia can occur in a wide variety of diseases due to a functional renal impairment or renal anoxia (Zondek, 1948; Maegraith, Havard & Parsons, 1945).

Such causative conditions as burns, crushing injuries, surgical shock and general infections such as Weil's disease can cause extra-renal azotaemia and it is conceivable that this might occur a few hours before death when the pulse becomes almost imperceptible, blood pressure falls, and a state of circulatory collapse occurs. The terminal rise in blood urea and plasma phosphorus, and the almost complete absence of chlorides in the urine could be explained on these grounds.

Against this is the fact that the ammonia content of the urine steadily rises, and the concentration in the specimen withdrawn by catheter at death is usually higher than that of the previous 24 hours.

The urine withdrawn at death, however, probably represents the secretion over the previous 5 - 8 hours, and if, for example, functional renal failure occurred two hours before death, the ammonia content of the total specimen

would not be a true reflection of the state of affairs obtaining in the final two hours.

In Case No. 11 it has been possible to show that the ammonia concentration of the urine at death (66.4 vols. N/10 per 100 ccs.) was lower than that found three hours before death (77.2 vols. N/10 per 100 ccs.).

Also in Case No. 21, the urine at death showed a lower concentration of ammonia than 24 hours previously, 36.8 vols. against 53.4 vols.

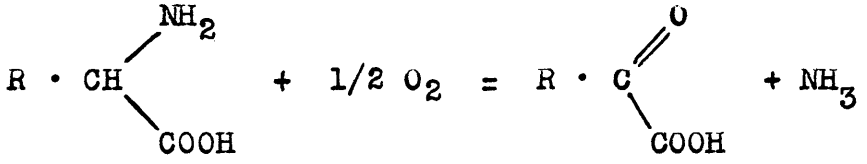
The conclusion drawn from these figures is that the ability of the kidneys to produce ammonia had become impaired at some point between the taking of the two respective specimens.

The experimental findings of Kempner (1939) would appear to support the conclusion made above. He set out to measure the effect of oxygen tension on the oxidative de-amination of amino acids in kidney tissue, and found that below an oxygen tension of 60 mms. Hg. (which is about the normal value in the kidneys under physiological conditions) the rate of de-amination was markedly dependent on variations of oxygen tension.

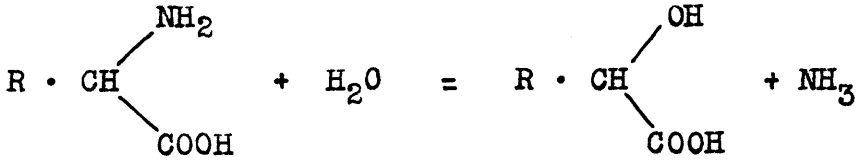
Since de-amination of amino acids is the main source of urinary ammonia (Krebs, 1933), renal anoxia leads

to disturbance of the acid/base equilibrium in the body. The condition, however, is reversible, and deamination can be restored to normal by increase in the oxygen available to the kidney cells.

Baldwin (1947) considers that the vast bulk of evidence relating to animal metabolism is in favour of an oxidative process of de-amination, depicted thus:



On the other hand, an alternative method is available, namely hydrolysis:



It is doubtful, however, if the body can make use of the hydrolytic process to a sufficient degree to offset the effects of anoxia (Baldwin, 1947).

In the author's cases, the circulatory collapse along with diminishing oxygenation of the blood make it probable that functional renal failure does occur several hours before death.

On these grounds it is justifiable to ascribe the terminal rise of blood phosphorus to phosphate retention following renal failure.

The other explanation of the rise in the level of blood phosphorus has been mentioned in previous chapters, namely, that which occurs during periods of anaerobic metabolism.

It has been shown that inorganic phosphorus is set free from the enzyme system phosphagen - adenosine triphosphate during anaerobic activity, and Jervell (1928) has demonstrated an increase of inorganic phosphorus in the blood in persons subjected to severe exercise. The rise, however, was small (in one case from 2.99 to 4.0 mgms. per cent.) and it does not seem that the rise of plasma phosphorus at death can be wholly ascribed to the anaerobic metabolism which occurs at this time.

It is more likely that both mechanisms - failure of renal function plus anaerobic metabolism - are together responsible for the sudden rise of plasma phosphorus during the 24 hours before death.

The results for plasma and urinary chlorides in the present work conform to those which would be found in any respiratory or metabolic acidosis, and therefore fit into

the general pattern of an agonal acidosis. Apart from a small terminal rise in plasma chloride which is thought to be due to haemoconcentration, the general level tends to be low during the last few days of life. The low level can be explained (a) by the chloride shift from plasma to corpuscles, (b) the low dietary salt intake to which patients who are dying are usually subject, and (c) in the tuberculous patients, by loss of chloride in perspiration.

In health the relation between blood and urinary chloride is fairly constant, the concentration in the urine being approximately double that of the blood. Wright (1940) states that chloride excretion in the urine ceases when the plasma level falls below 520 mgms. per cent.

In disease, however, the chloride threshold varies and the factors governing the variations are still not completely understood. For example, chloride continues to be excreted in diabetic acidosis and chronic renal disease even when the plasma concentration has reached very low levels, and conversely urinary chloride excretion remains infinitesimal when the plasma chloride is very high in pyloric stenosis or the hyperpnoea of encephalitis lethargica (Graham & Morris, 1933).

McCance & Young (1941) have shown that sodium and chloride clearance by the kidneys of new-born infants is very

low, even when the plasma values are very high.

Wilkinson et al. (1949) studied the urinary excretion of chlorides in the post-operative period and found it extremely low for about six days after operation despite the fact that 10 g. sodium chloride per day was given orally. At the same time there was a negative nitrogen balance, and they consider that chloride retention is in some way connected with the "katabolic phase" described by Cuthbertson (1948).

As death approaches the excretion of chloride becomes less and less and is probably a reflection of the falling level of plasma chloride. This explanation seems reasonable and may be accepted until the question of chloride metabolism and excretion is more fully understood.

Of all the constituents of the blood examined in dying patients, the blood urea alone seems to be unrelated to the changes found in the others, except possibly in the last 24 hours of life. It has been shown that the level of the blood urea is substantially above normal for about ten days before death in the average of the cases studied. The sharp rise found in the last specimen of blood examined at death is likely to be due to the terminal renal insufficiency, which has been discussed in previous pages. The explanation of this rise in blood urea level is offered by Kempner (1939). He says: "Urea is the end product of de-

amination of amino-acids in the liver, as is ammonia in the kidney. If the kidney's power of de-amination is impaired, the portion of amino-acids normally handled by the healthy kidney is offered to the liver and converted there into surplus urea; therefore the blood urea must rise."

To summarise, the rise in blood urea which takes place several days before death is due to pyrexia and a diminished intake of food leading to excessive tissue breakdown. The sharper rise which occurs in the immediate pre-agonal phase is probably due to super-added extra-renal azotaemia.

It would appear from the evidence found in the present investigation that the level of blood urea is independent of the degree of acidosis.

Hansen was also unable to demonstrate any correlation between agonal acidosis and nitrogenous substances in the blood, and concluded that it was not the fall in pH itself which causes increased tissue breakdown.

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An attempt has been made in this chapter to trace the development of the changes in blood biochemistry up to the time of death and show their correlation with a gradually increasing anoxaemia.

The anoxaemia which is initially determined by a failing respiratory centre and muscular weakness causes in turn deranged cellular respiration with increase in lactic and phosphoric acids; this in turn causes a fall in the plasma bicarbonate, thus calling into action the accessory mechanisms for dealing with an alteration in the acid/base balance of the body, namely the excretion of acids as ammonium salts by the kidneys, and the chloride shift between plasma and corpuscles.

The respiratory element in the production of the terminal acidosis, namely carbon dioxide retention, is assumed to exist, although not experimentally demonstrated in the present investigations.

When respiration becomes laboured and irregular, and the normal excursion lessened, gaseous exchange in the pulmonary alveoli is interfered with, leading on the one hand to anoxaemia and on the other to carbon dioxide retention in the blood. The alveolar carbon dioxide tension rises and so consequently does the carbon dioxide tension of the blood in order that diffusion of the gas may take place across the alveolar membrane. Carbon dioxide is an easily diffusible gas, however, and the pressure difference between blood and alveolus need only be quite small - about 6 mms. Hg. - in order that a moderate degree of diffusion of carbon dioxide may take place (Wright, 1940).

The physiological response to increase in blood carbon dioxide is hyperventilation, but this mechanism is not available to the patient who is dying, because the respiratory centre is exhausted. If it is not already so, it rapidly fails to respond to the stimulus.

It may be mentioned here that the majority of the patients studied in this series were receiving morphine several days before death, thus further depressing the respiratory centre (Linhard, 1911; Prescott et al., 1949).

The observation by Sir Lauder Brunton in 1901 that the dying patient slips away anaesthetised by his own carbon dioxide may well be true.

The hyperbilirubinaemia which occurs in the immediate pre-agonal period was discovered by chance during the course of the investigations. It is not a feature of acidosis per se, and no reference to its occurrence could be found in the literature pertaining to diabetic acidosis or in the experimental acidosis induced by ammonium chloride (Morris & MacRae, 1930). It does, however, seem to be related to anoxaemia, as the graphs in the present investigation show. The rise in the bilirubin level of the blood is a well recognised phenomenon in congestive cardiac failure, and its fall to normal levels consequent on recovery and efficient oxygenation of the blood has been demonstrated in Cases A and B in the Appendix.

The origin of the bilirubinaemia has already been discussed in a previous chapter; it is thought to be due to depression of the function of the reticulo-endothelial cells of the liver by anoxia (Rich & Resnik, 1926; Kugel & Lichtman, 1933).

CHAPTER IX.

THERAPY

The aim of therapy in disease is, whenever possible, directed towards the eradication of the primary lesion causing the disease. In the pre-terminal state, the aim of therapy should be directed at keeping the patient alive long enough for more specific measures against the primary cause of the morbidity to take effect.

Unfortunately, in the present series of cases, the cause of morbidity was such that no specific therapy could be applied to its eradication. The majority of patients were suffering from advancing tuberculosis, and the remainder from inoperable carcinoma, severe valvular disease of the heart and cerebral haemorrhage.

Nevertheless, in a small minority of cases it might be possible by the application of certain measures, to keep a patient alive until the primary disease is brought under

control. Diseases such as acute primary pneumonia and certain types of septicaemia respond well to penicillin and drugs of the sulphonamide series, but some patients die before specific therapy has a chance to take effect, usually because of late diagnosis.

What measures can be taken to prolong life? It has been shown in the results of the present investigation that anoxia is the primary cause of the metabolic changes which occur during the last 24 hours of life; it directly causes a metabolic acidosis, and in addition, due to carbon dioxide retention, a gaseous acidosis. The respiratory centre ceases to respond to the stimulus of carbon dioxide excess and oxygen lack, and thus further aggravates the acidosis.

It would seem, therefore, that the efficient administration of oxygen should be sufficient to break the vicious circle. It would allow normal cellular metabolism to proceed with the formation of no excess of acid metabolites such as lactic acid. Because of a lowered alveolar carbon dioxide tension, it would allow the passage of excess blood carbonic acid across the capillary-alevolar membrane, and so to be exhaled.

If the respiratory centre has already been exhausted before oxygen therapy is commenced, its irritability may be restored temporarily by the administration of coramine

or one of the allied drugs. Coramine used vigorously is a valuable drug in conditions such as have been described.

In extreme cases it may be advisable to correct an already established acidosis by the administration of an alkaline solution intravenously.

Koehler et al. (1925) prolonged the life of pigs appreciably by administering a sodium bicarbonate solution intravenously after a severe acidosis had been produced by anoxia.

Intravenous sodium bicarbonate has been used in the treatment of diabetic acidosis, but was dropped because it is a difficult solution to sterilise, but also because equivalent results could be obtained by using saline and insulin and allowing the body to correct the acidosis by physiological means.

Nevertheless, when speed is the keynote, and when the physiological processes of the body are depressed, the infusion of a small amount of alkaline fluid to a nearly moribund patient might help greatly in augmenting a decreased alkali reserve until the effects of oxygen administration are fully established.

Hansen also advocates the use of respiratory stimulants in the pre-agonal state, where there is hope of saving the patient by specific means. He describes the case

of a woman suffering from bilateral pneumonia whose general condition was very bad, but whose respiratory centre was kept active for the first 24 hours with a total dosage of 57 ml. Coramine. Thereafter the pneumonia, which was caused by the Type I pneumococcus, responded satisfactorily to the administration of sulphathiazole.

Hansen also used oxygen therapy, and intravenous 1.3% sodium bicarbonate solutions in several of his cases but gives no detailed results except to say that it seemed to have a temporary good effect and prolonged life longer than was expected. Most of Hansen's cases were similar to the author's in that the nature of the primary illness made death inevitable.

Arising from the results obtained in the present investigation contra-indications in therapy may be mentioned.

It is common practice to administer acid salts such as ammonium chloride prior to mersalyl injections in cases of severe cardiac failure with oedema. In such cases of cardiac failure examined in this series it was found that an acidosis of moderate degree already exists when dyspnoea and venous congestion are evident. The plasma bicarbonate is slightly lowered, the blood lactic acid is raised, and the urinary pH depressed. By giving acid forming salts in the doses advocated, an already established acidosis will be

increased dangerously, and the life of an ill patient imperilled.

It is therefore thought unnecessary to administer acid salts prior to giving mersalyl in cases of severe congestive cardiac failure with oedema.

When oxygen is administered to moribund patients in an effort to prolong life, it is very important to make sure that the cylinder does not contain a percentage of carbon dioxide, since there is already an increased carbon dioxide tension in the blood of such patients. Oxygen gas alone should be the therapy of choice.

The question of morphine administration also requires consideration.

In advanced pulmonary tuberculosis with hopeless prognosis morphine is almost a specific for the uncomfortable dyspnoea which occurs several days before death. Its use certainly keeps the patient comfortable and the frantic gasping for breath is greatly diminished. Morphine used in this way is justifiable, since the ultimate death of the patient is inevitable.

The foregoing remarks also apply to diseases such as inoperable cancer and others having a hopeless prognosis.

In fulminating infections like pneumonia, septicaemia, or acute meningococcal meningitis where the patient

is collapsed, it would be wiser to withhold morphine and use a respiratory stimulant until specific therapy has had time to act.

In milder cases of pneumonia, especially with severe pleural pain, it is justifiable to administer morphine, especially during the first 24 hours. Diminution of pleural pain alone will help to increase the respiratory excursion.

Morphine is undoubtedly beneficial in certain types of cardiac trouble, for example cardiac asthma and the pain of coronary thrombosis. On the other hand, when a patient is admitted to hospital with severe congestive cardiac failure and orthopnoea it would be proper not to depress the respiratory centre with morphine and so cause further carbon dioxide retention and increased acidosis. The rational therapeutic approach would be to administer oxygen efficiently and digitalise the patient quickly. If the patient required a sedative, one which does not act on the respiratory centre should be chosen.

To sum up, it may be said that whenever there is reasonable hope that life might be saved in a desperate case, nothing should be done which has the effect of increasing acidosis, either by oral medication or administration of morphine. In the case with hopeless prognosis, morphine should not be withheld.

CHAPTER X.

CONCLUSIONS

In patients dying of chronic diseases, no great changes in the blood or urine biochemistry can be detected up to within two or three days of death, with the exception of the blood urea.

The rise in the blood urea level is independent of the changes in the other blood constituents and seemed to depend on increased katabolism due to pyrexia, and a diminished food intake. This rise is seen often as early as ten days before death.

The pattern of biochemical changes which occurs in the two or three days before death shows an increasing tendency towards acidosis, which is most apparent in the final specimens of blood and urine taken immediately after death.

The primary cause of the pre-agonal acidosis is anoxia, which is produced by weakness of the respiratory muscles and exhaustion of the respiratory centre. A vicious circle is set up in which anoxia causes acidosis which in turn further interferes with efficient oxygenation of the tissues. Carbon dioxide retention occurs due to deficient pulmonary ventilation, and this combined with increased acid metabolites in the blood produces a mixed type of acidosis.

Several hours before death renal function becomes impaired due to anoxia of the kidney cells, and it is thought that this phenomenon explains the sharp increase in acidosis found at death.

It is suggested that an irreversible change occurs in the respiratory enzyme structure of the tissue cells shortly before death, leading to the production of large amounts of lactic acid. The damaging agent is most likely to be the toxic products of the disease process.

If the primary lesion causing the disease is treatable and the patient has reached an almost moribund state, immediate measures should be directed towards preventing or correcting acidosis. Oxygen should be given by an efficient method, and the excitability of the respiratory centre should be increased by giving Coramine. In desperate

cases a small amount of intravenous sodium bicarbonate solution might be useful as an additional measure.

A P P E N D I X

(a) TABULATED RESULTS
INDIVIDUAL CASES.

Case No. 1.

Date	June47 9th	18th	23rd	25th	26th	27th	29th		
Number of days before death	20	11	6	4	3	2	-		
" " hours " "									
Plasma Bilirubin mgms.%									
Plasma Bicarbonate mgms.%									
Hb.% (100% ≡ 14 g.%)									
Venous 0_2 Sat. CCS/100 CCS.									
Plasma Chlorides mgms.%									
Plasma Phosphorus mgms%	1.4	2.7					5.3		
Blood Lactic Acid. mgms.%									
Blood Urea. mgms.%									
Serum Calcium mgms.%	9.8	10.1					10.4		
Plasma Proteins g.%		4.68					5.11		
URINE.									
pH.		5.2		5.2	5.4	5.5	5.0		
Ammonia. Vols. N/10 %.			60.8		77.6		85.4		
Tit.Acidity Vols. N/10 %.			65.0		34.8		78.3		
Chlorides grammes/litre.									

	Case No. 2				Case No. 3				
Date	July 47 2nd	3rd	4th		June 47 25th	26th	27th	28th	
Number of days before death	3	2	1		3	2	1		
" " hours " "			10						
Plasma Bilirubin mgms.%									
Plasma Bicarbonate mgms.%	30.2		35.4		68.0			56.0	
Hb.% (100% ≡ 14 g.%)									
Venous 0_2 Sat. CCS/100 CCS.									
Plasma Chlorides mgms.%									
Plasma Phosphorus mgms%	2.3		3.7		2.2			6.4	
Blood Lactic Acid. mgms.%									
Blood Urea. mgms.%									
Serum Calcium mgms.%	10.4		10.7		9.7			10.2	
Plasma Proteins g.%									
URINE.									
pH.	5.9	5.6	5.8		6.7	6.4	5.9	5.4	
Ammonia. Vols. N/10 %.	82.8		118		44.4	72.8		100.0	
Tit.Acidity Vols. N/10 %.	35.6		56		13.6	37.6		57.2	
Chlorides grammes/litre.									

	Case No. 4				Case No. 5			
Date	July.47 3rd	4th	5th	5th	July 47 8th	9th	10th	11th
Number of days before death " " hours " "	2	1	3	-	3	2	1	-
Plasma Bilirubin mgms.%								
Plasma Bicarbonate mgms.%	52.0			49.3	53.2			45.9
Hb.% (100% ≡ 14 g.%)								
Venous 0_2 Sat. CCS/100 CCS.								
Plasma Chlorides mgms.%					573.0			511.0
Plasma Phosphorus mgms%	2.4			2.7	2.6			8.7
Blood Lactic Acid. mgms.%								
Blood Urea. mgms.%								
Serum Calcium mgms.%	10.1			10.6	9.8			8.3
Plasma Proteins g.%					6.7			7.2
URINE.								
pH.	5.0	5.2	5.4	5.2	5.7	5.7	5.7	4.9
Ammonia. Vols. N/10 %.	90.8	111.2		94.4	126.0		103.6	144.8
Tit.Acidity Vols. N/10 %.	101.2	71.6		90.4	74.0		55.6	115.6
Chlorides grammes/litre.								

	Case No. 6					Case No. 7		
Date	Aug.47 4th	5th	6th	7th	7th	Aug.47 25th	26th	27th
Number of days before death " " hours " "	3	2	1	- 3	-	2	1	-
Plasma Bilirubin mgms.%								
Plasma Bicarbonate mgms.%	41.4				38.0	42.5		33.6
Hb.% (100% ≡ 14 g.%)								
Venous 0_2 Sat. CCS/100 CCS.								
Plasma Chlorides mgms.%	550.0				522.0	550.0		518.0
Plasma Phosphorus mgms%	3.5				3.1	4.0		4.6
Blood Lactic Acid. mgms.%								
Blood Urea. mgms.%								
Serum Calcium mgms.%	10.8				10.2	9.8		8.9
Plasma Proteins g.%	6.4				5.8	7.2		6.8
URINE. pH.	5.2	5.1	5.2	5.1	4.7	4.7	5.1	4.6
Ammonia. Vols. N/10 %.	46.4	79.2	60.4		84.0	18.4		20.8
Tit.Acidity Vols. N/10 %.	64.0	52.0	69.6		76.0	28.0		28.8
Chlorides grammes/litre.	1.1			1.3	0.2	1.5		0.1

	Case No. 8			Case No. 9				
Date	July 47 9th		Aug. 47 8th		Nov. 47 3rd	3rd	3rd		
Number of days before death " " hours " "	30		-		8	4	-		
Plasma Bilirubin mgms.%									
Plasma Bicarbonate mgms.%	48.8		25.7		42.5	41.4	38.4		
Hb.% (100% ≡ 14 g.%)									
Venous 0_2 Sat. CCS/100 CCS.									
Plasma Chlorides mgms.%	611.0		593.0		582.0		524.0		
Plasma Phosphorus mgms%	1.8		4.3		2.0		4.9		
Blood Lactic Acid. mgms.%									
Blood Urea. mgms.%									
Serum Calcium mgms.%	10.4		9.6						
Plasma Proteins g.%	4.6		3.9						
URINE. pH.					5.8	5.2	4.8		
Ammonia. Vols. N/10 %.					32.1		87.7		
Tit.Acidity Vols. N/10 %.					16.6		69.3		
Chlorides grammes/litre.									

Case No. 10

Date	Oct.47 16th	17th	21st						
Number of days before death " " hours " "	5	4	-						
Plasma Bilirubin mgms.%									
Plasma Bicarbonate mgms.%	54.3		32.0						
Hb.% (100% ≡ 14 g.%)									
Venous 0_2 Sat. CCS/100 CCS.									
Plasma Chlorides mgms.%	594.0		638.0						
Plasma Phosphorus mgms%	2.2		3.1						
Blood Lactic Acid. mgms.%									
Blood Urea. mgms.%	62.0		188.0						
Serum Calcium mgms.%	10.5		10.8						
Plasma Proteins g.%									
URINE. pH.	4.7	4.8	4.6						
Ammonia. Vols. N/10 %.									
Tit.Acidity Vols. N/10 %.									
Chlorides grammes/litre.									

Case No. 11.

Date	Aug.47 6th	8th	11th	13th	16th	18th	18th		
Number of days before death " " hours " "	12	10	7	5	2	- 3	-		
Plasma Bilirubin mgms.%									
Plasma Bicarbonate mgms.%	65						68.3		
Hb.% (100% ≡ 14 g.%)									
Venous 0_2 Sat. CCS/100 CCS.									
Plasma Chlorides mgms.%	576.0						499.0		
Plasma Phosphorus mgms%	2.2						2.6		
Blood Lactic Acid. mgms.%									
Blood Urea. mgms.%									
Serum Calcium mgms.%									
Plasma Proteins g.%	5.8						5.0		
URINE. pH.	7.1	6.6	5.7	5.5	5.8	5.4	5.3		
Ammonia. Vols. N/10 %.	37.6	33.2				77.2	66.4		
Tit.Acidity Vols. N/10 %.	8.8	14.4				41.2	33.2		
Chlorides grammes/litre.		10.2					2.3		

Case No. 12.

Date	Sep.47 11th	12th	16th	17th	18th	20th	25th	26th
Number of days before death " " hours " "	15	14	10	9	8	6	1	-
Plasma Bilirubin mgms.%								
Plasma Bicarbonate mgms.%	47.0	47.0	44.0	37.0	34.0	33.6	34.0	32.0
Hb.% (100% ≡ 14 g.%)								
Venous 0_2 Sat. CCS/100 CCS.								
Plasma Chlorides mgms.%	587.0	584.0	596.0	587.0	590.0	596.0	649.0	673.0
Plasma Phosphorus mgms%	1.7			2.1				5.2
Blood Lactic Acid. mgms.%								
Blood Urea. mgms.%								
Serum Calcium mgms.%								
Plasma Proteins g.%	6.7			6.3				6.4
URINE.								
pH.	5.1	5.2	5.1	5.1	5.1	5.0	4.9	4.7
Ammonia. Vols. N/10 %.								
Tit.Acidity Vols. N/10 %.								
Chlorides grammes/litre.	7.3		3.3	4.2		0.3	0.2	0.1

Case No. 13

Date	Nov.47 24th	25th	26th	Dec.47 28th	1st	15th	22nd	27th	29th
Number of days before death " " hours " "	25	24	23	21	18	14	7	2	- 5
Plasma Bilirubin mgms.%	0.1	0.1	0.1	0.2	0.6	0.9	1.0	1.3	2.1
Plasma Bicarbonate mgms.%	51.5	43.6	39.4	45.3	42.5	44.8	48.1	43.0	40.2
Hb.% (100% ≡ 14 g.%)									
Venous 0_2 Sat. CCS/100 CCS.									
Plasma Chlorides mgms.%	601.0	603.0	596.0	585.0	608.0	620.0	611.0	574.0	556.0
Plasma Phosphorus mgms%									
Blood Lactic Acid. mgms.%									
Blood Urea. mgms.%									
Serum Calcium mgms.%									
Plasma Proteins g.%	6.4	6.1	6.1	5.7	6.1	5.2	5.4	5.5	5.1
URINE. pH.									
Ammonia. Vols. N/10 %.									
Tit.Acidity Vols. N/10 %.									
Chlorides grammes/litre.									

Case No. 14

Date	Dec.47 23rd	26th	30th	Jan48 6th	19th	20th	22nd		
Number of days before death " " hours " "	30	27	23	18	3	2	-		
Plasma Bilirubin mgms.%			0.1		0.43		0.5		
Plasma Bicarbonate mgms.%			62.0		58.2		61.1		
Hb.% (100% ≡ 14 g.%)									
Venous 0_2 Sat. CCS/100 CCS.									
Plasma Chlorides mgms.%			562.0		575.0		584.0		
Plasma Phosphorus mgms%			1.4		1.8		2.1		
Blood Lactic Acid. mgms.%									
Blood Urea. mgms.%									
Serum Calcium mgms.%									
Plasma Proteins g.%									
URINE. pH.	7.0	7.8	6.9	6.6	6.2	6.6	5.8		
Ammonia. Vols. N/10 %.									
Tit.Acidity Vols. N/10 %.									
Chlorides grammes/litre.									

	Case No. 15					Case No. 16		
Date	Nov.47 20th	20th	20th	21st	21st	May.48 23rd	July 48. 1st	4th
Number of days before death " " hours " "	2 32	2 27	1 15	- 5	-	41	3	-
Plasma Bilirubin mgms.%						1.2	3.8	4.3
Plasma Bicarbonate mgms.%	40.3		28.8		31.3	59.3	48.1	41.6
Hb.% (100% ≡ 14 g.%)						100.0	77.0	85.0
Venous 0_2 Sat. CCS/100 CCS.						4.4	4.1	1.3
Plasma Chlorides mgms.%	591.0		567.0		522.0	540.0	567.0	579.0
Plasma Phosphorus mgms%	3.6		3.9		8.7	2.5	2.9	5.9
Blood Lactic Acid. mgms.%						9.0	20.0	27.0
Blood Urea. mgms.%						50.0	80.0	75.0
Serum Calcium mgms.%								
Plasma Proteins g.%								
URINE.								
pH.	4.7	4.7	4.7	4.7	4.6	7.1	5.2	5.0
Ammonia. Vols. N/10 %.	50.2	52.0	56.0		82.3	8.2	48.0	67.6
Tit.Acidity Vols. N/10 %.	48.3	54.8	57.2		78.9	3.8	39.6	54.3
Chlorides grammes/litre.	2.5	2.3	2.1		0.3	3.7	0.87	0.2

	Case No. 17			Case NO.18		Case No. 19	
Date	May 48 27th	June 48 4th	18th	May 48 25th	27th	June 48 4th	7th
Number of days before death " " hours " "	21	14	-	2	-	3	-
Plasma Bilirubin mgms.%	2.1	2.8	4.5	0.9	1.7	0.7	1.8
Plasma Bicarbonate mgms.%	60.0	54.0	47.0	43.0	41.4	48.2	44.3
Hb.% (100% ≡ 14 g.%)	66.0	63.0	72.0	38.0	30.0	68.0	65.0
Venous 0_2 Sat. CCS/100 CCS.	5.6	3.9	Nil	0.3	Nil	5.4	Nil
Plasma Chlorides mgms.%	547.0	563.0	508.0	608.0	600.0	556.0	512.0
Plasma Phosphorus mgms%	2.3	2.7	6.9	1.9	2.8		
Blood Lactic Acid. mgms.%	17.0	18.0	67.0	15.0	30.0		
Blood Urea. mgms.%	35.0	35.0	90.0	60.0	110.0	75.0	100.0
Serum Calcium mgms.%	.	.	.				
Plasma Proteins g.%							
URINE. pH.	5.6	5.8	5.2			5.5	5.1
Ammonia. Vols. N/10 %.	46.0	52.3	65.5			16.4	46.9
Tit.Acidity Vols. N/10 %.	50.0	54.4	72.4			16.4	54.3
Chlorides grammes/litre.	2.4	2.2	0.32			1.15	Nil

	Case No. 20.		Case No. 21.			Case No. 22	
Date	June 48 4th	7th	June 48 4th	5th	6th	June 48 19th	22nd
Number of days before death " " hours " "	3	-	2	1	-	3	-
Plasma Bilirubin mgms.%	2.3	4.4	1.1		4.8	0.8	2.5
Plasma Bicarbonate mgms.%	48.3	45.0	52.0		37.0	52.2	43.6
Hb.% (100% ≡ 14 g.%)	54.0	72.0	32.0		47.0	65.0	59.0
Venous $\emptyset_2$ Sat. CCS/100 CCS.	8.4	0.1	3.5		1.6	8.9	0.2
Plasma Chlorides mgms.%	563.0	614.0	572.0		602.0	559.0	538.0
Plasma Phosphorus mgms%	2.6	5.5	3.7		18.2	2.1	6.6
Blood Lactic Acid. mgms.%							
Blood Urea. mgms.%	40.0	25.0	40.0		95.0	25.0	45.0
Serum Calcium mgms.%							
Plasma Proteins g.%							
URINE. pH.			5.9		5.1	6.6	5.6
Ammonia. Vols. N/10 %.			52.6	53.4	36.8	42.3	78.0
Tit.Acidity Vols. N/10 %.			31.4	35.5	36.8	28.5	69.6
Chlorides grammes/litre.	2.9	1.3	3.4	1.9	0.79	5.6	0.94

	Case No. 23		Case No. 24		Case No. 25		
Date	June 48 7th	8th	June 48 23rd	25th	June 48 29th	July 48. 1st	2nd
Number of days before death	1	-	2	-	3	1	-
" " hours " "						12	
Plasma Bilirubin mgms.%			0.5	2.9	0.4	1.5	3.2
Plasma Bicarbonate mgms.%	49.0	46.0	51.0	46.0	61.6	53.1	36.9
Hb.% (100% ≡ 14 g.%)	93.0	121.0	49.0	50.0	72.0	67.0	78.0
Venous 0_2 Sat. CCS/100 CCS.	8.2	1.2	4.8	Nil	4.5	3.8	Nil
Plasma Chlorides mgms.%	444.0	456.0	556.0	514.0	576.0	545.0	522.9
Plasma Phosphorus mgms%	2.3	3.6	1.7	5.7	2.08	3.7	10.4
Blood Lactic Acid. mgms.%			21.0	62.9	27.0	32.0	119.0
Blood Urea. mgms.%	160.0	130.0	45.0	70.0	40.0	50.0	55.0
Serum Calcium mgms.%							
Plasma Proteins g.%							
URINE. pH.	5.5	5.0	5.5	5.2	5.8	5.6	5.4
Ammonia. Vols. N/10 %.	72.3	94.1	72.2	131.6	62.8	60.2	77.2
Tit.Acidity Vols. N/10 %.	55.2	98.0	48.2	128.2	40.4	52.4	71.6
Chlorides grammes/litre.	6.5	3.9	3.6	0.8	3.5	2.2	1.75

Date	Case No. 26 July 48 8th	10th	18th	Case No. 27 July 48 8th	10th	17th
Number of days before death " " hours " "	10	8	-	9	7	-
Plasma Bilirubin mgms.%	0.45	0.4	2.6	0.1	0.1	9.7
Plasma Bicarbonate mgms.%	52.0	54.0	38.0	62.0	65.1	43.2
Hb.% (100% ≡ 14 g.%)	71.0	67.9	55.0	94.0	83.0	68.0
Venous 0_2 Sat. CCS/100 CCS.	7.9	8.1	0.2	11.3	10.1	Nil
Plasma Chlorides mgms.%	570.0	585.0	534.0	586.0	580.0	519.0
Plasma Phosphorus mgms%	2.1	2.2	8.5	2.8	2.5	6.8
Blood Lactic Acid. mgms.%						
Blood Urea. mgms.%	75.0	70.0	110.0	75.0	75.0	95.0
Serum Calcium mgms.%						
Plasma Proteins g.%						
URINE. pH.	6.5	6.2	5.1	5.6	6.7	4.8
Ammonia. Vols. N/10 %.	15.4	18.2	63.2	81.2	77.7	122.3
Tit.Acidity Vols. N/10 %.	6.3	7.1	66.7	62.4	58.2	112.4
Chlorides grammes/litre.	8.1	7.4	0.3	5.2	4.8	0.1

	Case No. 28.		Case No. 29		Case No. 30
Date	July 48 8th	10th	Oct. 48. 19th	20th	Decr. 48 5th
Number of days before death " " hours " "	2	-	1	-	-
Plasma Bilirubin mgms.%	1.3	1.8	0.34	2.5	1.4
Plasma Bicarbonate mgms.%	54.0	56.0	64.8	55.4	
Hb.% (100% ≡ 14 g.%)	55.0	59.0	61.0	70.0	83.0
Venous 0_2 Sat. CCS/100 CCS.	2.2	0.2	8.0	1.6	0.3
Plasma Chlorides mgms.%	574.0	562.0	573.0	562.0	503.0
Plasma Phosphorus mgms%	2.9	4.1	2.1	4.3	2.6
Blood Lactic Acid. mgms.%	18.0	22.5	18.6	75.0	86.0
Blood Urea. mgms.%	35.0	50.0	30.0	35.0	45.0
Serum Calcium mgms.%					
Plasma Proteins g.%					
URINE. pH.	5.5	5.3			5.3
Ammonia. Vols. N/10 %.	45.2	67.9			82.6
Tit.Acidity Vols. N/10 %.	35.6	58.3			77.3
Chlorides grammes/litre.	4.5	1.1			0.58

	Case No. 31.			Case No. 32			
Date	May 48 25th	June 48 4th	20th	Novr.48 6th	8th	9th	9th
Number of days before death " " hours " "	25	16	-	3	1	- 1	-
Plasma Bilirubin mgms.%	0.7	1.1	3.2	0.1	0.2	1.0	1.3
Plasma Bicarbonate mgms.%	46.4	43.1	33.2	54.3	44.2	39.3	38.0
Hb.% (100% ≡ 14 g.%)	72.0	64.0	62.0	53.0	52.0	67.0	73.0
Venous 0_2 Sat. CCS/100 CCS.	8.3	6.4	Nil	6.7	5.8	3.1	0.3
Plasma Chlorides mgms.%	591.0	574.0	532.0	542.0	555.0	562.0	591.0
Plasma Phosphorus mgms%	1.7	1.7	5.9	2.5	2.7	3.0	4.2
Blood Lactic Acid. mgms.%				21.0	32.0	75.0	45.0
Blood Urea. mgms.%	25.0	35.0	70.0	70.0	85.0	125.0	180.0
Serum Calcium mgms.%							
Plasma Proteins g.%							
URINE. pH.	6.0	6.4	5.2	6.0	5.8	5.3	5.1
Ammonia. Vols. N/10 %.	52.4	42.8	99.1	34.3	42.4	33.2	17.1
Tit.Acidity Vols. N/10 %.	31.6	19.6	78.3	14.2	23.1	42.4	20.2
Chlorides grammes/litre.	5.26	5.67	0.8	0.7	0.18	0.3	1.1

	Case No. 33		Case No. 34				
Date	Novr. 48 1st	2nd	Oct.48 27th	Novr.48. 2nd	4th	6th	7th
Number of days before death " " hours " "	1	-	10	5	3	1	-
Plasma Bilirubin mgms.%	0.7	0.9	1.2	2.3	3.7		3.7
Plasma Bicarbonate mgms.%	37.2	31.6	42.0	43.2	39.1		35.3
Hb.% (100% ≡ 14 g.%)	48.0	53.0	72.0	85.0	76.0		82.0
Venous 0_2 Sat. CCS/100 CCS.	6.7	0.3	Nil	10.5	Nil		Nil
Plasma Chlorides mgms.%	546.0	514.0	503.0	527.0	562.0		557.0
Plasma Phosphorus mgms%	2.8	6.4	2.2	1.9	5.8		8.2
Blood Lactic Acid. mgms.%	25.0	67.0	72.0	38.0	60.0		111.0
Blood Urea. mgms.%	55.0	75.0	80.0	95.0	120.0		95.0
Serum Calcium mgms.%							
Plasma Proteins g.%							
URINE. pH.	5.4	4.9					
Ammonia. Vols. N/10 %.	39.2	28.7					
Tit.Acidity Vols. N/10 %.	19.3	24.9				0.41	
Chlorides grammes/litre.	2.1	0.5					

During O_2 therapy.

	Case No. 35			Case No. 36				
Date	Novr.48 15th	18th	21st	Novr.48 17th	23rd			
Number of days before death " " hours " "	9	6	3	6	-			
Plasma Bilirubin mgms.%	0.4	0.5	0.7	0.4	1.8			
Plasma Bicarbonate mgms.%	64.5	59.3	57.4	48.3	42.1			
Hb.% (100% ≡ 14 g.%)	94.0	92.0	87.0	64.0	52.0			
Venous 0_2 Sat. CCS/100 CCS.	10.9	7.9	3.7	8.6	1.7			
Plasma Chlorides mgms.%	572.0	567.0	575.0	608.0	523.0			
Plasma Phosphorus mgms%	2.0	2.2	2.0	1.8	5.6			
Blood Lactic Acid. mgms.%	17.0	29.0	27.0	15.0	62.0			
Blood Urea. mgms.%	50.0	115.0	100.0	40.0	65.0			
Serum Calcium mgms.%								
Plasma Proteins g.%								
URINE. pH.	6.1	6.0	5.4	5.6	5.1			
Ammonia. Vols. N/10 %.				32.6	89.1			
Tit.Acidity Vols. N/10 %.				14.1	67.4			
Chlorides grammes/litre.	5.73	4.39	2.32	5.31	0.76			

	Case No. 37				Case No. 38		
Date	Novr.48 18th	28th	Decr.48 3rd	7th	Novr.48 27th	28th	28th
Number of days before death " " hours " "	20	9	4	-	1	- 9	-
Plasma Bilirubin mgms.%	0.4		0.3	0.9	1.4	1.3	1.5
Plasma Bicarbonate mgms.%	57.2		49.8	46.0	38.4	39.0	28.0
Hb.% (100% ≡ 14 g.%)	65.0		56.0	75.0	76.0	82.0	91.0
Venous 0_2 Sat. CCS/100 CCS.	7.1		5.7	Nil	Nil.	0.4	Nil
Plasma Chlorides mgms.%	582.0		558.0	538.0	532.0	541.0	562.0
Plasma Phosphorus mgms%	1.7		2.1	3.5	3.6	3.8	5.3
Blood Lactic Acid. mgms.%	28.0		19.0	79.0	47.0	52.0	71.0
Blood Urea. mgms.%	40.0		65.0	40.0	85.0	95.0	90.0
Serum Calcium mgms.%							
Plasma Proteins g.%							
URINE. pH.	5.7	5.7	5.8	5.4	5.8	5.4	5.1
Ammonia. Vols. N/10 %.	12.7	29.7	44.3	67.6	64.3	61.7	51.1
Tit.Acidity Vols. N/10 %.	6.2	13.6	21.7	59.8	52.4	48.7	53.2
Chlorides grammes/litre.	1.28	4.21	2.63	0.23	1.46	0.99	0.56

	Case No. 39			Case No. 40				
Date	Decr.48 12th	14th	15th	Decr.48 13th	15th	17th	22nd	24th
Number of days before death " " hours " "	3	1	-	11	9	7	2	-
Plasma Bilirubin mgms.%	1.3	1.4	0.8	0.6			1.1	3.7
Plasma Bicarbonate mgms.%	49.2	44.0	37.1	48.0			46.9	38.2
Hb.% (100% ≡ 14 g.%)	58.0	66.0	69.0	81.0			61.0	69.0
Venous 0_2 Sat. CCS/100 CCS.	5.3	0.6	Nil	6.3			1.72	0.2
Plasma Chlorides mgms.%	550.0	554.0	620.0	547.0			486.0	562.0
Plasma Phosphorus mgms%	2.0	2.4	2.9	1.75			2.3	3.7
Blood Lactic Acid. mgms.%	13.0	24.0	41.0	15.0			27.0	74.0
Blood Urea. mgms.%	20.0	35.0	50.0	35.0			135.0	150.0
Serum Calcium mgms.%								
Plasma Proteins g.%								
URINE.								
pH.	6.6	5.9	5.7	6.4	6.3	5.9	5.6	5.0
Ammonia. Vols. N/10 %.	32.7	52.7	67.2	42.7	38.7	44.8	55.3	78.1
Tit.Acidity Vols. N/10 %.	12.9	31.2	56.1	24.0	21.6	26.2	29.0	69.5
Chlorides grammes/litre.	0.7	0.56	0.35	3.11	0.52	0.05	1.93	3.27

	Case No. 41			Case 42.			
Date	Jan.49 6th	7th	11th	Jan.49 8th			
Number of days before death " " hours " "	5	4	-	-			
Plasma Bilirubin mgms.%	1.3	0.9	2.4	5.3			
Plasma Bicarbonate mgms.%	42.0	40.3	33.6	24.3			
Hb.% (100% ≡ 14 g.%)	70.0	68.0	74.0	72.0			
Venous 0_2 Sat. CCS/100 CCS.	7.6	7.9	Nil	Nil			
Plasma Chlorides mgms.%	585.0	563.0	597.0	515.0			
Plasma Phosphorus mgms%	2.3	2.7	4.8	7.5			
Blood Lactic Acid. mgms.%	33.0	30.0	42.0	67.0			
Blood Urea. mgms.%	70.0	65.0	70.0	100.0			
Serum Calcium mgms.%							
Plasma Proteins g.%							
URINE. pH.	6.0	5.7	5.6	4.9			
Ammonia. Vols. N/10 %.	18.3	22.7	47.1	111.4			
Tit.Acidity Vols. N/10 %.	7.4	10.9	44.6	98.0			
Chlorides grammes/litre.	4.2	3.74	1.11	0.17			

Case No. 43

Date	Jan.49 11th	12th	13th	19th	23rd	26th	27th		
Number of days before death " " hours " "	16	15	14	8	4	1	-		
Plasma Bilirubin mgms.%	0.9					7.2	8.5		
Plasma Bicarbonate mgms.%	65.3					55.2	48.3		
Hb.% (100% ≡ 14 g.%)	81.0					78.0	84.0		
Venous 0_2 Sat. CCS/100 CCS.	3.9					1.3	Nil		
Plasma Chlorides mgms.%	551.0					562.0	532.0		
Plasma Phosphorus mgms%	2.8					4.7	6.3		
Blood Lactic Acid. mgms.%	26.0					28.0	46.0		
Blood Urea. mgms.%	55.0	45.0	60.0	65.0	75.0	70.0	65.0		
Serum Calcium mgms.%									
Plasma Proteins g.%									
URINE.									
pH.	5.7	5.4	5.4	5.4	5.3	5.3	4.7		
Ammonia. Vols. N/10 %.	52.0	44.2	72.6	76.7	84.6	97.8	102.8		
Tit.Acidity Vols. N/10 %.	37.0	31.3	55.9	64.4	81.1	87.6	93.2		
Chlorides grammes/litre.	1.1	0.4	1.1	3.8	1.11	0.81	0.41		

	Case No. 44					Case No. 45	
Date	Dec.48 1st	19th	Jan.49 28th	31st	Feb.49 11th	Jan.48 27th	29th
Number of days before death " " hours " "	73	23	14	11	-	2	-
Plasma Bilirubin mgms.%	0.35			0.8	2.2	0.32	1.6
Plasma Bicarbonate mgms.%	51.0			47.2	31.3	52.2	59.0
Hb.% (100% ≡ 14 g.%)	56.0			48.0	57.0	97.0	111.0
Venous 0_2 Sat. CCS/100 CCS.	3.3			4.2	0.4	11.5	0.1
Plasma Chlorides mgms.%	567.0			569.0	542.0	622.0	581.0
Plasma Phosphorus mgms%	2.5			2.7	5.8	2.1	6.9
Blood Lactic Acid. mgms.%	17.0			18.0	84.0		
Blood Urea. mgms.%	70.0			20.0	95.0		
Serum Calcium mgms.%							
Plasma Proteins g.%							
URINE. pH.	6.9	7.2	6.7	6.2	5.1	5.8	5.3
Ammonia. Vols. N/10 %.						21.5	69.7
Tit.Acidity Vols. N/10 %.						9.7	58.2
Chlorides grammes/litre.	5.2		0.87	3.85	0.2	6.3	1.3

Case No. 46

Date	Sept.48 6th	7th	9th	10th	11th	12th	13th		
Number of days before death " " hours " "	7	6	4	3	2	1	-		
Plasma Bilirubin mgms.%	0.15	0.2	0.2	0.3	1.75	2.4	2.6		
Plasma Bicarbonate mgms.%									
Hb.% (100% ≡ 14 g.%)									
Venous 0_2 Sat. CCS/100 CCS.									
Plasma Chlorides mgms.%	1.6	1.9	2.0	1.9	2.6	2.5	6.8		
Plasma Phosphorus mgms%									
Blood Lactic Acid. mgms.%	10.0	12.0	21.0	25.0	37.0	44.0	87.0		
Blood Urea. mgms.%									
Serum Calcium mgms.%									
Plasma Proteins g.%									
URINE.									
pH.	5.9	5.7	5.8	5.7	5.4	5.1	4.8		
Ammonia. Vols. N/10 %.	21.7	18.2	23.6	31.6	44.0	72.8	98.0		
Tit.Acidity Vols. N/10 %.	8.4	4.5	8.1	14.5	26.1	48.9	88.6		
Chlorides grammes/litre.	9.2	7.8	8.8	5.2	2.1	0.9	0.2		

	Case No. 47		Case No. 48
Date	Nov.48 4th	5th	Jan.49 29th
Number of days before death " " hours " "	1	-	-
Plasma Bilirubin mgms.%	0.8	1.9	1.7
Plasma Bicarbonate mgms.%	32.1	24.7	34.7
Hb.% (100% ≡ 14 g.%)			57.0
Venous 0_2 Sat. CCS/100 CCS.			Nil.
Plasma Chlorides mgms.%	543.0	522.0	515.0
Plasma Phosphorus mgms%	1.9	3.8	5.7
Blood Lactic Acid. mgms.%	32.0	68.0	58.0
Blood Urea. mgms.%	65.0	135.0	125.0
Serum Calcium mgms.%			
Plasma Proteins g.%			
URINE.			
pH.	5.7	4.9	4.9
Ammonia. Vols. N/10 %.	56.2	83.7	77.8
Tit.Acidity Vols. N/10 %.	48.1	56.6	72.1
Chlorides grammes/litre.			0.18

	Case No. 49				Case No. 50			
Date	Nov.48 14th	17th	22nd	27th	Nov.48 5th			
Number of days before death	13	10	5	-	-			
" " hours " "								
Plasma Bilirubin mgms.%	0.2	0.3	0.8	2.2	0.7			
Plasma Bicarbonate mgms.%	57.3	52.0	46.1	35.0	37.8			
Hb.% (100% ≡ 14 g.%)					69.0			
Venous $\emptyset_2$ Sat. CCS/100 CCS.					0.7			
Plasma Chlorides mgms.%	591.0	572.0	543.0	496.0	531.0			
Plasma Phosphorus mgms%	1.9	1.7	2.0	6.9	3.9			
Blood Lactic Acid. mgms.%	13.0	17.0	19.0	84.0	48.0			
Blood Urea. mgms.%	30.0	30.0	35.0	65.0	85.0			
Serum Calcium mgms.%								
Plasma Proteins g.%								
URINE.								
pH.	7.2	6.8	6.3	5.1	5.2			
Ammonia. Vols. N/10 %.								
Tit.Acidity Vols. N/10 %.								
Chlorides grammes/litre.	5.27	4.3	1.92	0.42	0.7			

Normal Controls.

Date	A.C.B. 23.8.47	M.S. 15.12.47	J.B. 4.6.48	I.F. 25.11.48	E.C. 18.1.49	W.R. 20.1.49			
Plasma Bilirubin mgms.%	0.2	Nil	0.5	0.4	0.1	0.3			
Plasma Bicarbonate mgms.%	59.0	62.0	65.0	57.0	60.0	55.0			
Hb.% (100% ≡ 14 g.%)	-	-	105.0	98.0	95.0	103.0			
Venous 0_2 Sat. CCS/100 CCS.	-	-	10.2	8.4	7.6	9.7			
Plasma Chlorides mgms.%	618.0	591.0	596.0	602.0	587.0	611.0			
Plasma Phosphorus mgms%	1.8	2.3	2.0	2.5	1.9	2.1			
Blood Lactic Acid. mgms.%	-	-	18.0	15.0	20.0	22.0			
Blood Urea. mgms.%	20.0	20.0	25.0	30.0	20.0	30.0			
Serum Calcium mgms.%	11.1	10.4	-	-	-	-			
Plasma Proteins g.%	6.8	7.0	-	-	-	-			
URINE.									
pH.	6.8	7.3	6.3	5.8	6.7	6.0			
Ammonia. Vols. N/10 %.	8.4	3.2	6.8	10.4	1.6	8.4			
Tit.Acidity Vols. N/10 %.	3.6	1.6	4.0	6.8	0.8	5.8			
Chlorides grammes/litre.	7.4	6.8	8.2	5.6	6.6	7.1			

1. Plasma Bilirubin.

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.
Mgms.%	2.75	1.69	1.03	1.24	0.55	1.46	0.36	0.57

Days before death.	8.	9.	10.	11.	13.	14.	16.	18.
Mgms.%	0.4	0.4	0.65	0.7	0.2	1.8	0.9	0.6

Days before death.	20.	21.	23.	24.	25.
Mgms.%	0.4	1.15	0.1	0.1	0.4

2. Plasma Bicarbonate.

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Vols. CO_2%	41	42	48	50	45	46	47	56	44	54	48

Days before death.	11.	12.	13.	14.	15.	16.	18.	20.	21.	23.	24.
Vols. CO_2%	48	65	57	48	47	59	43	57	53	51	44

Days before death	25.
Vols. CO_2%	49

3. Haemoglobin

Days before death.	Death	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Percent.	70	69	55	68	62	77	78	83	67	94	71
Days before death	11.	14.	16.	20.	21.	25					
Percent.	64	63	72	65	66	72					

4. Oxygen Saturation

Days before death.	Death	1.	2.	3.	4.	5.	6.	7.	8.	9.	10
Ccs. per 100 Ccs.	0.6	4.2	4.0	5.9	6.8	9.1	8.4	10.1	8.1	11.2	3.9
Days before death	11.	14.	16.	20.	21.	25.					
Ccs. per 100 Ccs.	5.3	3.9	5.1	7.1	5.6	8.3					

5. Plasma Chlorides

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.	8.
Mgms. %	571.	549	581	562	565	562	590	595	587

Days before death.	9.	10.	11.	12.	13.	14.	15.	16.	18.
Mgms. %	581	560	558	576	591	589	587	563	608

Days before death.	20.	21.	23.	24.	25.
Mgms. %	582	566	579	603	596

6. Plasma Phosphorus.

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.	8.	9.
Mgms. %	5.6	2.8	2.6	2.6	2.3	2.1	1.9	2.5	2.2	2.3

Days before death.	10.	11.	12.	13.	14.	15.	16.	20.	21.	23.
Mgms. %	2.0	2.3	2.2	1.9	2.7	1.7	2.3	1.5	2.3	1.4

7. Blood Lactic Acid.

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.	9.	10.	11.
Mgms.%	65	37	24	27	23	30	18	10	17	45	12

Days before death.	13.	14.	16.	20.	21.
Mgms.%	13	18	26	28	17

8. Blood Urea.

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Mgms.%	87	78	63	63	67	65	77	75	67	62	61

Days before death.	11.	13.	14.	15.	16.	20.	21.	25.
Mgms.%	27	30	47	45	45	40	35	25

9. Serum Calcium

Days before death.	Death	1.	2.	3.	5.	11.	20.	30.
Mgms.%	9.8	10.7	10.0	10.2	10.5	10.1	9.8	10.4

10. Plasma Proteins.

Days before death.	Death	2.	3.	7.	9.	11.	12.	14.	15.
Grammes %.	5.44	6.4	6.4	5.4	6.3	4.68	5.8	5.2	6.7

Days before death.	18.	21.	23.	24.	25.	30.
Grammes %.	6.1	5.7	6.1	6.1	6.4	4.6

11. pH of Urine

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.	8.	9
pH.	5.08	5.4	5.5	5.8	5.4	5.8	5.8	6.0	5.6	5.7
Days before death.	10.	11.	12.	13.	14.	15.	16.	18.	20.	23
pH.	6.2	5.9	7.1	7.2	5.8	5.3	6.1	6.6	5.7	7.0
Days before death.	25.	27.	30.							
pH.	6.0	7.8	7.0							

12. Urinary Chlorides

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.	8.	9.
grammes/litre.	0.5	1.5	2.9	2.4	4.1	3.5	4.5	4.7	5.6	3.96
Days before death.	10.	11.	13.	14.	15.	16.	20.	21.	25.	
grammes/litre.	6.5	3.5	5.3	1.4	3.8	3.4	1.3	2.4	5.3	

13. Ammonia in Urine

Days before death.	Death.	1.	2.	3.	4.	5.	6.	7.
Vols. n/10 per 100 ccs.	77.3	64.2	57.4	54.6	44.0	18.0	37.0	48.3
Days before death.	8.	9.	10.	11.	12.	14.	15.	16.
Volts. n/10 per 100 ccs.	47.5	50.0	24.0	42.0	38.0	52.0	44.0	47.4
Days before death	20.	21.	25.					
Vols. n/10 per 100 ccs.	13.0	46.0	52.0					

14. Titratable Acidity of Urine.

Days before death.	Death	1.	2.	3.	4.	5.	6.	7.
Vols. n/10 per 100 ccs.	68.4	46.2	44.7	34.1	30.2	7.0	27.6	30.6
Days before death.	8.	9.	10.	11.	12.	14.	15.	16.
Vols. n/10 per 100 ccs.	35.5	32.6	10.0	24.0	9.0	54.0	31.0	28.3
Days before death.	20.	21.	25.					
Vols. n/10 per 100 ccs.	6.0	50.0	31.0					

(c) [illegible].

Case 1. S.J. Male. Age 40. Admitted : 30.5.47.
Died : 29.6.47.

The patient gave a history of lumbar pain since January 1947. This was accompanied by increasing breathlessness on exertion and cough. After a severe bout of vomiting on 27/5/47, he was admitted to Glasgow Royal Infirmary.

On admission, he was seen to be a thin restless man, rather pale and dyspnoeic, having a frequent cough and abundant sputum. There was no clubbing of the fingers, koilonychia or palpable glands.

Examination of the chest revealed wasting, impaired percussion note and cavernous breathing with sticky creps at the right apex. Xray of chest confirmed a large cavitating lesion at the right apex, and the sputum on direct smear revealed numerous tubercle bacilli.

On 9/6/47 the patient appeared fairly comfortable and was not dypnoeic at rest. However, after another week it was evident that there was considerable deterioration. Respirations had become hurried and were 34 per minute.

On 25/6/47 he had become semicomatose but could be roused to answer questions, but from this date his condition rapidly deteriorated and he died on 29/6/47.

The temperature had been intermittent since the day of admission, but became subnormal 12 hours before death.

Cardiac puncture was performed immediately after death.

Diagnosis : Pulmonary Tuberculosis.

Case 2. W.R. Male Age 52 Admitted : 16.6.47.
Died : 5.7.47.

The patient was admitted to Glasgow Royal Infirmary for chest investigation.

He gave a history of having had a cough and loss of weight for three months previously. A few weeks before admission he had a small haemoptysis, followed by another a few days later.

On admission, the patient was orthopnoeic and showed some distress, but with rest in bed this settled down. He was

pale and had lost a lot of weight, and there were signs of a pulmonary lesion on the right side. Xray of chest confirmed the presence of the lesion which clinically and radiologically was a bronchial carcinoma.

By the time the first blood and urine specimens were taken on 2/7/49, the patient had again become very distressed and was obviously failing.

Dyspnoea persisted until death.

The last specimens were taken 10 hours before death.

Diagnosis : Bronchial Carcinoma.

Case 3. D.P. Male. Age 15. Admitted : 19.6.47
Died : 28.6.47

The patient was admitted as a case of acute appendicitis to the Surgical Wards of Glasgow Royal Infirmary, but no operation was performed because of atypical history and signs.

He had a convulsion on the evening of 20.6.47 and thereafter transferred to the Medical Wards on 21.6.47.

His condition on transfer was poor; he was in a semi-comatose state, but could be roused, and complained of headache.

Examination revealed that he had bilateral palsy of the external recti muscles, papilloedema, and an extensor plantar response on the left side.

There was a loud blowing systolic murmur at the apex, but no signs of cardiac failure.

Abdominal examination was negative, and there was no abnormality of the urine.

Lumbar puncture produced a clear fluid under pressure, and the following was the pathological report.

a. No growth of Tb on culture.
b. Cell count of 50/c.m.m. - mixed polymorphs and lymphocytes.
c. Protein 95 mgms%.
d. Chloride 529 mgms%

The condition was considered to be tuberculous meningitis.

Progress : Deterioration was steady day by day and coma deepened. The breathing was of the Cheyne-Stokes type for 24 hours before death.

Blood was taken by cardiac puncture immediately after death.

Diagnosis : Tuberculous Meningitis.

Case 4. J.McG. Male. Age 32. Admitted : 26.6.47
Died : 5.7.47

The patient was admitted to the Medical Wards with a history of dyspnoea and chest pain of 7 weeks duration.

The first sign of his present illness was in 1940 when he was discharged from the Army because of a "bad heart". He had had repeated attacks of rheumatic fever since he was 11 years old.

After discharge from the Army he found work as a labourer, but was continually off work due to dyspnoea.

On admission, the patient was distressed, breathless and cyanosed. His liver was 3 fingers breadth enlarged below the right costal margin. His spleen was not palpable, and there was no oedema.

The pulse was regular and rapid - 120 per minute. The apex beat was palpable 6" to the left in the 6th interspace.

Systolic and diastolic murmurs were easily heard at both apex and base, and indicated disease if both mitral and aortic valves.

His condition settled a little after admission, but thereafter he gradually deteriorated. The dyspnoea became more pronounced and he had repeated haemoptyses.

He died at 1 p.m. on 5.7.47, and blood was taken immediately from the jugular vein, and the bladder emptied by catheter.

Diagnosis : Congestive cardiac failure.
Rheumatic carditis.

Case 5. W.F. Male. Age 40. Admitted : 12.6.47
Died : 11.7.47

The patient on admission complained of pain in the right side of chest of 6 weeks duration; also a lump growing on the right side of chest and left side of neck.

He had lost only a little weight and was very slightly dyspnoeic on exertion.

On examination the patient was found to be a strong well built man, who had not apparently lost much weight. Physical signs in the chest were those of a right pleural effusion and the tumours on the chest wall were firm, hard and not tender, and appeared to be fixed to the deep tissues.

Straight Xray of chest and tomograph showed collapse of the right middle lobe and a right pleural effusion. Biopsy of the tumour confirmed that it was neoplastic.

The condition then, was bronchial carcinoma with secondaries.

The patient's general condition began to deteriorate very rapidly; flesh was quickly lost; he became anaemic and breathless.

On 4.7.47 he received one massive dose of deep Xray therapy, but with no noticeable effect.

By the time the first biochemical estimations were made, the patient was extremely dyspnoeic; the temperature was slightly raised, and he was receiving Morphine at night.

Blood was removed from the heart immediately after death.

Post Mortem confirmed the diagnosis of right bronchial carcinoma with secondaries in the tissues of the anterior chest wall, and left supraclavicular glands. There were a few small secondaries in the liver.

Diagnosis : Bronchial Carcinoma.

Case 6. K.C. Male. Age 27. Admitted : 24/7.47.
Died : 7.8.47.

This patient gave a history of increasing breathlessness of one month's duration. During the war he served as a

paratrooper, and was taken Prisoner of War at Arnheim. He was discharged from the Army in November 1945 with a label of "neurosis", but there was no note of any cardiac lesion on his papers. He had remained well apart from bronchitis until the present illness commenced.

He had mumps and measles in childhood, but there was no history of rheumatic fever, chorea, or growing pains.

Examination revealed a pale man of medium build; he was very dyspnoeic, and had slight oedema of the ankles.

The heart was enlarged and there was a loud diastolic murmur at the aortic area and down the left border of the sternum. An Austin-Flint murmur was well heard at the apex.

The W.R. and Kahn tests were negative.

The liver was enlarged and tender, and the spleen was easily palpable 2" below the left costal margin. He was running a temperature, but this gradually settled with 0.5 mega units of Penicillin per day. The spleen also became gradually smaller.

Although it appeared that the infection was being controlled, the valvular lesion was so gross that the patient became gradually more and more dyspnoeic and died on 7.8.47.

Blood was removed immediately by cardiac puncture.

Post Mortem confirmed sub-acute bacterial endocarditis superimposed on a congenital bicuspid aortic valve.

Diagnosis : Sub-acute Bacterial Endocarditis.
Congestive Cardiac Failure.

Case 7. B.S. Female. Age 59. Admitted : 23.8.47
Died : 27.8.47

The history was of nocturnal dyspnoea of 7 month's duration, which had become much worse during the two weeks before admission.

She had been practically confined to bed for the last 6 months because of breathlessness on exertion and oedema of the ankles, and paroxysmal nocturnal dyspnoea was often severe. Recently the symptoms became much worse and she began to vomit and the dyspnoea became continuous.

There was no previous history of nephritis and kidney function was little impaired, but she had suffered a stroke 5 years previously which left her right side weak.

On examination, the patient was orthopnoeic, cyanosed and had oedema of the ankles and puffy eyes.

The pulse was regular, 98 per minute, and the blood pressure = 240/135. The apex beat was 5" from the midsternum in the 5th left interspace. The lungs were clear except for moist rales at both bases.

The clinical picture was of cardiac failure following hypertension.

The patient gradually became more comatose, and finally developed Cheyne-Stokes breathing 24 hours before death.

Blood was taken immediately by cardiac puncture.

Post Mortem. The left internal capsule showed signs of an old haemorrhage, and the gall bladder was full of calculi. The left ventricle was grossly enlarged.

Diagnosis : Cardiac failure.

Case 8. H.McC. Male. Age 38. Admitted: 20.4.47
Died : 8.8.47

This man was admitted to the Medical Wards of Glasgow Royal Infirmary with a transverse myelitis of fairly sudden onset. There was no improvement in either the motor or sensory loss which extended from the hips donwards, and bedsores of huge dimensions soon developed.

He remained alive for nearly four months gradually becoming weaker and weaker due to toxic absorption from the extensive bedsores. His was a protracted and slow death over many weeks, and he was pyrexial most of the time.

The urine became infected at an early stage, and an indwelling catheter was fitted. No accurate biochemical analysis could be made of the urine because of the heavy infection.

Blood was removed by cardiac puncture immediately after death.

Diagnosis · Transverse Myelitis.

Case 9. P.D. Male. Age 47. Admitted : 24.10.47
Died : 3.11.47

The patient was semi-comatose on admission, but could be roused to answer questions. The only history which could be elicited was that he had developed a severe headache a few days prior to admission. The night before being admitted to the Medical Wards of Glasgow Royal Infirmary, he had had his stomach washed out and admitted to the Casualty Ward.

He presented as a well nourished and well built adult. There was no cyanosis or jaundice and the skin and mucus membranes were well coloured.

Blood pressure : 120/80.
Respirations : 20/minute.
Pulse : 84/minute.

The pupils were unequal in size and both plantar responses were extensor, and there was moderate spasticity of both lower limbs.

Lumbar puncture produced a blood stained cerebro spinal fluid. On 2.11.47 the respirations began to rise up to 40/minute and the following day they were 60/minute with the pulse running at 144/minute. He fell into a deep coma and became incontinent, but the urine could be collected.

Two hours before death the respirations began to get slower and became Cheyne-Stokes in character.

The final blood sample was taken by cardiac puncture immediately after death.

Diagnosis : Subarachnoid Haemorrhage.

Case 10. T.H. Male. Age 76. Admitted : 4.9.47.
Died : 21.10.47.

At the beginning of July 1947 the patient had an attack of jaundice which lasted three weeks. According to his own Doctor's Notes his liver was enlarged three fingers breadth. The jaundice slowly cleared but the abdomen began to swell and weight was rapidly lost. The ankles also became oedematous.

On admission to the Medical Wards of Glasgow Royal Infirmary on 4.9.47 the patient had a "muddy" complexion and had

lost a lot of weight. The peritoneal cavity was full of fluid, which, after paracentesis, enabled the liver to be felt about three fingers breadth below the costal margin. The spleen was not felt. There was a small pleural effusion on the right side but otherwise the lungs were healthy.

He remained fairly well until 6.10.47 when jaundice reappeared growing steadily deeper in hue. The other physical signs remained unaltered.

By 19.10.47 the patient had become very weak and semi-comatose. The breathing was slow, shallow, and laboured. This persisted until death on 21.10.47 at 12 noon. Blood for examination was obtained by cardiac puncture immediately after death.

Treatment given consisted of Morphine during the last four days, and he had also been having injections of 2 c.cs. of Mersalyl on alternate days, which were preceeded by several doses of Ammonium Chloride. The acid salt had no doubt influenced the level of the pH of the urine, and also the level of the plasma bicarbonate.

Post Mortem revealed a primary carcinoma of the body of the pancreas with one large secondary deposit in the liver.

Diagnosis : Carcinoma of Pancreas.

Case 11. D.B. Male. Age 50. Admitted : 30.7.47.
Died : 18.8.47.

This man complained of swelling of the left arm, huskiness of his voice and breathlessness of six week's duration.

He had suffered from bronchitis for many years but two months ago he developed a pain in the left side of his chest which lasted for a week but did not recur. The sputum had become copious and mucopurulent.

The patient's general condition on admission was fairly good; He appeared comfortable and showed no dyspnoea at rest. The physical signs and history suggested a carcinoma of the bronchus on the left side causing pressure on the left recurrent laryngeal nerve and subslavian veins.

On 6.8.47 when the investigation was started, the patient still remained comfortable and was not dyspnoeic. By 14.8.47 his general condition had obviously deteriorated and he was breathless. This gradually became worse and he died at 12 noon on 18.8.47.

Blood was taken by cardiac puncture immediately after death.

Post Mortem. There was a small contracted carcinoma of the left upper lobe bronchus with secondary pneumonic consolidation on the left side. There were secondary deposits in the glands below the left clavicle compressing the subclavian vein.

Diagnosis : Bronchial Carcinoma.

Case 12. E.S. Male. Age 58. Admitted : 29.8.47
Died : 26.9.47

This man had complained of dyspnoea for about 3 months before admission to Glasgow Royal Infirmary on 29.8.47. Since the breathlessness started, he has had an attack almost every night. During the day he was comfortable but had dyspnoea on exertion. He never had any oedema of the ankles, nor headaches.

There was nothing relevant in his previous or family history.

On examination, the patient appeared comfortable; there was no dyspnoea, cyanosis, or oedema. The pulse was regular, and the blood pressure = 210/135. The heart was enlarged, the apex beat being $5\frac{1}{2}$" from midsternum in the 5th left interspace. W.R. was negative. There was a trace of albumen and a few granular casts in the urine.

The patient remained fairly comfortable up to 11.9.47 although he still had nocturnal attacks of dyspnoea. The breathing became Cheyne-Stokes in character, and his general condition deteriorated thereafter. Three days prior to death he became comatose, and the respirations were very laboured. Cyanosis was marked, and the urinary output diminished. He died on 26.9.47.

Drugs given : Cardophyllin
Digitalis
Calcium Gluconate

Diagnosis : Hypertensive Cardiac Failure.

Case 13. R.R. Male. Age 67. Admitted : 13.11.47
Died : 29.12.47

The patient was admitted after having collapsed in the street. He was semi-comatose and completely aphasic.

In August 1947 he was investigated for anaemia, and a routine Xray of chest at that time revealed an opacity which was considered to be a neoplasm of a bronchus in the left side.

Four weeks before admission he had a cough and blood-stained sputum with periodic pain in the left chest.

His previous history revealed nothing relevant.

Examination revealed a pale man who had lost a lot of weight. He was not jaundiced and had no oedema or palpable glands. He was aphasic, and had a right sided hemiplegia. Blood Pressure = 100/70.

The aphasia gradually cleared up over a period of days, but the hemiplegia persisted.

The cerebro spinal fluid was not under pressure, clear, and showed no pathological changes.

Bed sores began to appear, and they became deep and necrotic.

It was evident that the patient's condition was deteriorating. He had always been slightly dyspnoeic since admission, but Cheyne-Stokes breathing was noted first on 4.12.47 and continued until death.

The illness was protracted.

No Post Mortem was performed, but the case was considered to be bronchial carcinoma with a secondary tumour of the brain.

No drugs given.

The last specimen of blood was taken 5 hours before death. No urine could be collected because of incontinence.

Diagnosis : Bronchial Carcinoma.

Case 14. J.H. Male. Age 57. Admitted : 4.12.47
Died : 22. 1.48

For two months this patient had complained of pain in the right side of the chest. The onset was gradual, and was more a dull ache than a sharp, pleuritic type of pain, and it was not constantly present. He had dyspnoea on exertion. A week before admission, the pain became more severe.

He had only a slight cough with a whitish sputum, and had noticed no bloodstaning. About one stone in weight had been lost since the illness commenced.

On admission, he looked a fairly well built man and had a plethoric facies. The fingers showed some clubbing. Clinical examination revealed signs of an effusion at the right base, and Xray confirmed this, showing also an opacity which was in keeping with the diagnosis of bronchial carcinoma.

Whilst in hospital, there was no sign of dyspnoea, and the general condition was good, although palpable nodules appeared on the scalp and enlarged glands could now be felt in the left axilla.

The patient's death on 22.1.48 was very sudden, occurring within the space of 15 minutes. He presumably had a cerebral catastrophe caused by secondary carcinomatous growth in the brain.

Because of his relatively good general condition whilst in hospital, and the sudden nature of his death, the biochemical findings did not differ in any way from the normal.

Blood was taken at death by cardiac puncture.

Diagnosis : Bronchial Carcinoma.
Cerebral Haemorrhage.

Case 15. J.M. Male. Age 52. Admitted : 20.11.47
Died : 21.11.47

This patient had syphilitic aortitis, and had been in hospital twice within recent months, April 1947 and July 1947. He had severe aortic incompetence with cardiac failure.

He was admitted for the third time on 20.11.47 complaining of severe precordial pain and breathlessness of two days duration.

Clinically, he was very dyspnoeic, and venous congestion was marked. The pulse was 90/minute, regular, and the apex beat was palpable 5" to the left of the midsternal line in the 6th interspace. There was a loud aortic diastolic murmur, and an Austin-Flint murmur at the apex.

The patient was pale and sweating and the accessory muscles of respiration were being brought into use, so great was the dyspnoea. He gradually became worse and died on 21.11.47, the day after admission.

Blood was obtained by cardiac puncture immediately after death.

Diagnosis : Cardiac failure.
Syphilitic Aortitis.

Case 16. W.S. Male. Age 41. Admitted : 23.1.46
Died : 4.7.48

The patient had a long history of cough, lassitude and loss of weight, and had been in hospital in 1945, from which he took his own discharge.

When admitted to Robroyston Hospital on 23.1.46, he complained of anorexia, night sweats, cough and copious sputum which was occasionally blood stained.

Xray of chest on 4.6.46 showed tuberculous disease in the greater part of both lungs with cavitation in the upper zones. Since that time he had remained well and regained some weight and strength on Sanatorium regime.

By 23.5.48, the patient was seen to be lying comfortably in bed with no dyspnoea at rest; he was rather thin and had a typical pink malar flush. He had been receiving regular doses of an alkaline mixture for indigestion.

On 1.7.48 it was obvious that his condition was beginning to deteriorate. Morphine had to be administered at night because of restlessness and discomfort in the chest. He became very drowsy and the respirations were weak and shallow.

On 4.7.48 the dyspnoea was more marked, and had been so for the past 48 hours. He had had several loose motions, and the effort of being lifted on and off a bed pan proved too much for him and he died at 1.35 p.m.

Cardiac puncture 5 minutes after death.

Diagnosis : Pulmonary Tuberculosis.

Case 17. M.C. Male. Age 48. Admitted : 27.5.48
Died : 18.6.48

The patient was admitted to Robroyston Hospital on 27.5.48, having been seen at a Tuberculosis Clinic in his district.

He gave a history of lassitude, loss of weight and cough, with an abundant sputum, of 6 month's duration. Xray of chest and sputum examination at the Clinic had confirmed that the condition was pulmonary tuberculosis, and he had been resting at home for several weeks prior to admission.

Clinically he was rather a spare, thin man, with a troublesome cough and a copious purulent sputum. He was seen to be slightly breathless even at rest.

Examination of the chest gave evidence of consolidation of the right upper half of the lung, with cavitation. There were a few sticky creps also heard in the left axilla. Xray confirmed the tuberculous consolidation of the right upper half and early infiltration in the left upper third.

Rest in bed over a period of weeks did not have much effect on the general condition. The pulse remained about 100 - 120 per minute, and the temperature never settled. He grew more breathless day by day, until for the last three days before death respirations were very laboured and shallow.

Cardiac puncture was performed 5 minutes after death.

Diagnosis : Pulmonary Tuberculosis.

Case 18. I.S. Female. Age 29. Admitted : 2.10.47.
Died : 27. 5.48.

There was a long history of abdominal upset; the patient had complained of abdominal pain and loose motions since June 1947, and she had been in various hospitals with suspected pelvis abscess, appendicitis, and finally tuberculous peritonitis was suspected.

On admission to Robroyston Hospital her condition was poor, and her skin was a pale colour with a lemon yellow tint. Clubbing of the fingers was present and she was very wasted.

On 24.10.47, she developed an ischio rectal abscess which ruptured, and remained patent until her death. At various times, urine and faeces were discharged through the sinus, and

it was also suspected that she had a recto-vesical fistula, because her urine was foul smelling and pussy, and occasionally faecal material was admixed with the urine.

The general condition steadily deteriorated. On clinical findings, tuberculous peritonitis was diagnosed; the abdomen was full and doughy to palpation and a mass was felt in the left iliac fossa.

When the first blood sample was taken on 25.5.48, the patient was extremely emaciated, but conscious. She died two days later on 27.5.48 at 11 a.m., and blood was withdrawn by cardiac puncture within 5 minutes.

There was no tuberculous lesion in the lungs, and the temperature during the last month of life averaged normal.

No urine estimations were possible due to contamination.

Diagnosis : Abdominal Tuberculosis.

Case 19. H.McC. Female. Age 21. Admitted : 2.6.48.
Died : 7.6.48.

This girl had been a known case of pulmonary tuberculosis since 1945, and had received treatment in Ruchill Hospital from 7.1.46 to 18.3.47. She had a right artificial pneumothorax and recovered sufficiently well enough for dismissal.

She was admitted to Robroyston Hospital on 2.6.48 in an extremely poor condition. She was grossly oedematous, the parts affected were the ankles, back and face, and respiratory distress was very marked.

Clinically there was chronic tuberculous disease of the right lung which was collapsed 2/3 in the upper zone and showed a hydropneumothorax. The left lung was fibrosed, but looked quiescent.

The sputum was positive for acid alcohol fast bacilli, and a 24 hour specimen of urine also showed the organism, confirming an infection of the renal tract.

There was no clinical improvement with rest in bed, and her condition steadily deteriorated. The respiratory rate, which was 25 per minute on admission steadily rose to 33 per minute by 6.6.48. Thereafter, the respirations became slower and the excursion shallower, until she died on 7.6.48.

Morphine was liberally administered during the last three days of life.

Cardiac puncture was performed 10 minutes after death.

Diagnosis : Pulmonary Tuberculosis.

Case 20. M.K. Female. Age 44. Admitted : 1.4.48.
Died : 7.6.48.

The patient developed a pain in the left side of the chest in April 1947 while nursing her daughter who had pulmonary tuberculosis.

During the following twelve months her health had deteriorated, she lost weight, felt tired, and had a troublesome cough with abundant sputum.

When admitted to Robroyston Hospital on 1.4.48, pulmonary tuberculosis was confirmed by Xray of chest and sputum examination.

There was active tuberculous disease in the upper 2/3 of the right lung, and considerable fibrosis of the left lung with mediastinal shift to the left. There was also a large cavity in the left upper 1/3.

Progress The general condition was poor, and she ran an irregular pyrexia which persisted until death. After a few day's bed rest dyspnoea was not noticeable, but for several days before death it became much more noticeable. Under the influence of Morphine, the respirations became very shallow and laboured, especially during the last 24 hours.

The urine was heavily infected, and this vitiated the estimation of pH and ammonia, but not the chlorides.

The patient was extremely emaciated at death, and had not taken food for several days.

Cardiac puncture was performed 10 minutes after death.

Diagnosis : Pulmonary Tuberculosis.

Case 21. A.S. Male. Age 21. Admitted : 7.8.47
Died : 6.6.48

The patient gave a history of pulmonary tuberculosis since 1942. He had been irregularly dismissed from another Sanatorium in July 1946 and had attended Baird Street. A.P. Clinic for refills of a left artificial pneumothorax which was

maintained satisfactorily with injections every six to eight weeks. At the end of June 1947, he experienced an acute and sudden attack of breathlessness, and readmission to hospital was arranged.

On admission his condition was only fair; he had a bad cough and copious sputum, and a pain in the left chest. He had a hydropneumothorax on the left side with a well defined fluid level, and aspiration at regular intervals was performed. The straw-coloured fluid eventually became infected, and a direct smear revealed numerous tubercle bacilli.

Up to 31.5.48, the pyopneumothorax was repeatedly aspirated, and after each aspiration 20 c.c.s of para-amino-salicylic acid was injected, without any clinical or bacterio-logical effect.

At this time, it was seen that his general condition was beginning to deteriorate rapidly; amyloid disease of the liver was present, and the abdomen became distended.

During the last 10 days, Morphine was liberally administered, and the breathing became shallow and noisy, and was accompanied by vigorous efforts by all accessory muscles of respiration.

The patient eventually died at 8.55 p.m. on 6.6.48. Cardiac puncture was performed immediately after death.

Diagnosis : Pulmonary Tuberculosis.

Case 22. T.McM. Male. Age 30. Admitted : 3.6.48
Died : 22.6.48

This man was admitted to Robroyston Hospital with a history of having had a cough off and on for two years, which had been getting worse. He had lost his voice two years previously, but had no pain in the throat. He had never had any bloodstaining of the sputum, which was, however, abundant.

He had been in the Army from 1939 and was discharged because of a gastric ulcer.

On admission, his general condition was very poor. He was thin, pale, and his breathing was distressed. There was cyanosis and clubbing of the fingers.

Examination of the chest, both clinically and by radiography, revealed very extensive and active tuberculosis of both lungs.

With bed rest, the patient settled down a little and the dyspnoea subsided, although the cough was very troublesome and the sputum copious.

On the evening of 21.6.48, the patient became more breathless, and this increased until the afternoon of 22.6.48 when he became comatose. Thereafter the respiratory excursion became less and the rate slower until he died at 11 p.m. on 22.6.48.

He had received no oral medication apart from a Codeine mixture, and he also had Omnopon by injection. The urine was free from albumin and sugar.

A blood sample was taken by cardiac puncture within 10 minutes of death.

Diagnosis : Pulmonary Tuberculosis.

Case 23. P.D. Female. Age 23. Admitted : 20.5.48
Died : 8.6.48

Headaches developed 10 days before admission, and became gradually worse. She was drowsy and complained of nausea and vomiting, and the appetite was lost.

These symptoms became more marked, and the headache became mainly occipital. There had been periods of mental confusion and delirium.

As a child, the patient had rheumatic fever.

She had pleurisy in 1942 which developed into pulmonary tuberculosis. In 1944 the patient was admitted to Robroyston Hospital with tuberculosis of the dorso lumbar spine and was discharged 2 years later in a plaster jacket.

The patient's general condition on admission was poor; she looked thin and toxic. The pulse rate was 58 per minute and there was a soft systolic murmur at the apex. There was slight nuchal rigidity.

Progress There was a rapid deterioration in her condition. The headache became very severe, and nuchal rigidity was more definite.

On 5.6.48 the pupils became irregular, and the patient was delirious. Morphine was commenced.

On 6.6.48 the respiratory excursions were noticeably

shallower, and breathing was laboured.

8.6.48. The patient was moribund; she had no food since admission, and very little fluid. It was evident that death was imminent. Cyanosis became extreme, and dyspnoea was marked just before death at 8.10 p.m.

Cardiac puncture was performed immediately.

Diagnosis : Tuberculous Meningitis.

Case 24. J.B. Female. Age 35. Admitted : 17.1.48
Died : 25.6.48

The first sign of illness was in January 1947 when the patient began to cough and spit. Since then, she became tired easily and lost weight.

In April 1947, the patient had a brisk haemoptysis, and the disease was discovered to be pulmonary tuberculosis after Xray of chest at her local Clinic.

Up to her admission to Robroyston Hospital on 17.1.48, she had remained indoors, resting in bed as much as possible.

Xray of chest showed extensive tuberculous disease in the right lung, especially in the upper half, which was active, and of the pneumonic type. Sputum - positive for acid and alcohol fast bacilli.

After a period of bed rest and general Sanatorium regime, the patient settled down; her temperature and pulse fell, and a little weight was gained. A right artificial pneumothorax was successfully induced on 21.4.48, and refills were continued with. It was evident, however, that this was not going to be successful because of dense adhesions, and it was decided to abandon it and subsequently perform a thoracoplasty. Unfortunately, the previous improvement was not maintained, and there was a fresh spread to the contralateral lung.

Toxaemia and dyspnoea became increasingly marked.

On 24.6.48, oxygen was given by nasal catheter, but no good effect was produced and it was discontinued. The dyspnoea was relieved much better by Morphine.

25.6.48. Patient moribund; dyspnoea was very severe, and

she died at 4 p.m.

Cardiac puncture was performed within 10 minutes of death.

Diagnosis : Pulmonary Tuberculosis.

Case 25. A.A. Male. Age 41. Admitted 26.6.48
Died 2.7.48

Eight weeks before admission to Robroyston Hospital on 26.6.48, the patient had complained of pain in both hips and was treated for neuritis. At the same time he had a bad cough with copious sputum, which was noted to be bloodstained on several occasions.

He admitted of having had a cough since December 1947, but said it had not troubled him sufficiently to seek advice.

On admission, the patient was in rather poor condition, pale, thin, and slightly dyspnoeic. The dyspnoea became somewhat less after a few days complete bed rest, but nevertheless was still evident.

On clinical examination, it was found that there was extensive involvement of the whole left lung and upper 1/3 of the right lung by an inflammatory process which was proved to be tuberculous on sputum examination.

The breathlessness suddenly became worse on the evening of 1.7.48, and he collapsed into semi-coma. The breathing became shallow and gradually weaker until he died at 6 a.m. on 2.7.48.

Cardiac puncture was performed 10 minutes after death. He had received no other drug treatment except Morphine, for two days before death.

Diagnosis : Pulmonary Tuberculosis.

Case 26. M.McC. Female. Age 37. Admitted:14.2.48
Died :18.7.48.

The patient developed a cough in June 1946 which was diagnosed as bronchitis by her family doctor. The cough did not respond to treatment, and she was sent for Xray, which revealed pulmonary tuberculosis, this being confirmed by sputum examination.

The Xray report, then, was that there was advanced fibro-caseous disease with cavitation on both sides.

On admission to Robroyston Hospital, her general condition was poor and did not seem to improve with Sanatorium regime.

During the last two months of life the temperature showed an evening rise, varying from 99° to 101°, which persisted until the last 24 hours before death when it became subnormal.

Dyspnoea at rest was a fairly marked feature, and this got worse during the last week of life.

The patient became semi-comatose on 17.7.48, finally lapsing into deep coma with Cheyne-Stokes breathing a few hours before death.

This patient had been receiving Morphine gr.$\frac{1}{4}$ daily for two months before death.

Cardiac puncture was performed immediately on death.

Diagnosis : Pulmonary Tuberculosis.

Case 27. J.C. Male. Age 42. Admitted : 28.6.48
Died : 17.7.48

The patient was admitted to Robroyston Hospital on 28.6.48 because of a cough, and because an Xray of chest as an Out-Patient showed a suspicious shadow at the left apex.

The general condition was excellent and there was no breathlessness. He had a troublesome cough and complained of pain in the left shoulder.

The sputum was repeatedly negative for acid-alcohol-fast bacilli, and further investigation was undertaken to determine the pathology of the pulmonary lesion.

Laryngoscopic examination revealed an adduction paralysis of the left vocal cord.

A bronchogram showed that the left upper lobe bronchus was blocked.

Carcinoma of the bronchus was diagnosed, and this was substantiated by the course of events. He had a convulsion on 2.7.48, never having had one before. Weight began to be lost rapidly, and dyspnoea became evident.

Three days before death it was noted that the sclerotics were becoming jaundiced, and next day this had become obvious on the skin.

During the stay in hospital there was no pyrexia. Morphia was administered during the last three days of life.

A blood sample was taken by cardiac puncture immediately after death.

Diagnosis : Bronchial Carcinoma.

Case 28. M.W. Female Age 26 Admitted : 24.6.48
Died : 10.7.48

The patient had been confined 8½ months previous to admission. Previous to this, in October 1947, she had had a slight haemoptysis, and an Xray of chest immediately afterwards, confirmed the diagnosis of pulmonary tuberculosis.

Just before admission to Robroyston Hospital on 24.6.48, she had another moderate haemoptysis.

On examination, she looked pale, toxic and cyanosed, with breathlessness at rest. The dyspnoea settled a little with complete bed rest, but her evening temperature consistently reached high levels, with an average of about 102°.

Her pulse rate was high.

An Xray of chest on 29.6.48 showed bronchopneumonic type of tuberculosis throughout the right lung and in the left lower half, the disease tending to become confluent. The lesion was very active. There appeared to be very little functioning lung tissue left.

The general condition deteriorated quickly, and during the last week of life dyspnoea was particularly marked. The distress, however, was controlled by liberal use of Morphine.

She became comatose 4 hours before death, which took place on 10.7.48.

Cardiac puncture was performed within 10 minutes of death.

Diagnosis : Pulmonary Tuberculosis.

Case 29. W.L. Male. Age 43. Admitted : 31.1.48
Died : 20.10.48

The patient was admitted to Robroyston Hospital on 31.1.48 having previously been in a Sanatorium for five months in 1943.

He had remained fairly well after discharge in 1943, but had noticed a deterioration in his health during the Summer of 1947. He complained of lassitude, troublesome cough and sweating at night, and was losing weight.

On examination, he was seen to be a heavily built adult, rather pale and showing signs of loss of flesh. He was pyrexial, and this continued until his death nine months later.

Xray of chest revealed extensive, active tuberculous disease in both lungs, mainly confined to the upper halves. There was a large cavity at the left apex and a smaller one in the first right interspace. The prognosis was poor, and conservative Sanatorium treatment was the only treatment possible.

The general condition gradually deteriorated; sputum was abundant and purulent, but there was no bloodstaining. In the last two months before death there was considerable deterioration.

On 19.10.48 it was noted that the patient was becoming drowsy and his pupils were unequal. Nuchal rigidity was present to a slight degree, and he was very irritable. Respirations were 25 per minute, and there was no obvious distress in breathing. It was considered that he had developed tuberculous meningitis.

On 20.10.48 the patient lapsed into coma and the respirations became Cheyne-Stokes in type, and were very shallow. He died at 11 a.m.

He had received Nembutal gr. 6 per day during the last four days of life.

Blood was removed immediately by cardiac puncture.

Diagnosis : Pulmonary Tuberculosis.
Tubercular Meningitis.

Case 30. P.N. Male. Age 19. Admitted : 29.9.48
Died : 5.12.48

This patient had been treated in another hospital since May 1947 where he had been admitted because of pleurisy. Pulmonary tuberculosis affecting the right lung was discovered after Xray of the chest.

He was treated by bed rest and received a course of Myocrisin, and later a right artificial pneumothorax was commenced but was subsequently abandoned.

He was transferred to Robroyston Hospital on 29.9.48.

His general condition was fair; he was rather thin, pale, and had a troublesome cough at night, the sputum being moderate in amount. Breathlessness was present only on exertion.

Xray of the chest on 4.10.48 showed a large cavity in the right upper third, and the remainder of the right lung was obliterated by pleural thickening. The left lung was congested but showed no tuberculous lesion.

In view of this report it was decided to embark on a right thoracoplasty, and the first stage was performed on 22.10.48, the first and third ribs being resected. The second stage was performed on 3.12.48, ribs four to seven being removed.

After leaving theatre, the patient collapsed. The pulse was rapid and "thready", dyspnoea was marked, and the tips of the ears, nose and lips were blue. Despite resuscitating measures, he remained in this condition for 48 hours, ultimately dying at 6.40 p.m. on 5.12.48.

His temperature had shown an evening rise of 101° for the last 10 days before death, and the drugs given were Coramine and Omnopon. Cardiac puncture was performed within 5 minutes of death.

Diagnosis : Pulmonary Tuberculosis.

Case 31. G.M. Male. Age 43. Admitted : 28.4.48.
Died : 20.6.48.

The patient had pleurisy in 1940 while serving in the Army.

In February 1948, he complained of pain in the chest accompanied by a cough. Eventually he had his chest Xrayed four weeks before admission, and pulmonary tuberculosis was discovered.

On admission, his general condition was very poor. He had a bad cough with abundant purulent sputum which showed numerous acid-acohol-fast bacilli on direct smear.

There were no signs of renal or abdominal tuberculosis.

The Xray report on the chest on 4.5.48 was "There is tuberculous disease in the right upper half and throughout the left lung. There is an apical pneumothorax on the left side with collapse of the left upper half of the lung. The disease on both sides is very active".

Progress . There was steady deterioration, and weakness was more evident about a month after admission (19.5.48). The breathlessness became more severe every day and especially so after bouts of coughing.

On 17.8.48 he was confused and tended to be drowsy. There was oedema of the feet and ankles, and cyanosis of the lips, nose and ears.

During the last 48 hours of life, dyspnoea became severe, and this gradually lapsed into the slow, shallow type of breathing so often seen in the terminal stages. He died in coma at 2.30 a.m. on 20.6.48.

His temperature had been swinging to 102° but there was a terminal fall to 97° in the last 24 hours.

Diagnosis : Tuberculous Bronchopneumonia.

Case 32. T.D. Male. Age 21. Admitted 20.10.48
Died 9.11.48.

The patient had a routine Xray of chest in the Navy after enlisting in 1945, and it was found that he had pulmonary tuberculosis. He was invalided, and attended a Tuberculosis Clinic as an Out-Patient.

He did no work for 15 months, but was taken on as a Mental Attendant in April 1947. About this time he got married.

In June 1948 he had an attack of "pneumonia", which did not clear up as expected; he began to lose weight and developed a bad cough with abundant sputum.

Soon afterwards he was re-Xrayed, and it was found that he had now developed extensive pulmonary tuberculosis.

He was admitted to Robroyston Hospital after having been confined to bed at home for several weeks.

The disease was extensive and bronchopneumonic in character, involving both lungs. He had a severe, painful laryngitis.

Progress. The patient was very ill, pale and emaciated. Rest in bed did not seem to have any beneficial effect, and his general condition was seen to deteriorate from day to day. The temperature was high and remittent until the day of death when it became subnormal.

No food was taken for three days before death, and very little fluid. Dyspnoea was not very marked until the day of death, when the typical fast, shallow respiration was seen, and this gradually changed to slow irregular breathing until the hour of death.

Morphine had been administered for 13 days prior to death.

Blood and urine were collected immediately after death.

Diagnosis : Pulmonary Tuberculosis.
Tuberculous Laryngitis.

Case 33. B.M. Female. Age 43. Admitted : 13.10.48
Died : 2.11.48

The patient had been in Gartloch Hospital 3 years previously with asthma, and again in Stobhill Hospital in September 1948, where pulmonary tuberculosis was diagnosed. She was transferred to Robroyston Hospital on 13.10.48.

She gave a history of having been unwell for about a year, with a vague feeling of lassitude, loss of weight, and slight cough.

The cough became worse and she had an abundant purulent sputum, and sweated profusely at nights.

He general condition was only fair, and it was obvious she had lost a considerable amount of weight. She was pale, but showed no obvious signs of distress.

Clinical examination revealed an active inflammatory process in the right upper half and throughout the left lung which was adjudged tuberculous on account of her positive sputum.

Progress The temperature was high remittent in character, and remained so until her death. Two days before death she developed oedema of the legs and sacral pad, and on the actual day of death, 6 hours before, she became semi-comatose, respiration was embarassed and she coughed up mouthfuls of pus. Cyanosis was marked for several hours before death.

She died at 2 p.m. on 2.11.48, and blood was collected immediately by cardiac puncture.

Morphine had been administered frequently for several days previous to death.

Diagnosis : Pulmonary Tuberculosis.

Case 34. M.McC. Female. Age 21. Admitted : 18.10.48
Died : 7.11.48

In 1946, after the birth of a child, the patient developed a cough and spit and felt languid; she lost her appetite.

Several months later she was admitted to Stobhill Hospital with pleurisy, but only remained for one week. Xray at that time revealed tuberculous disease in the left upper third, the right lung being clear. Deterioration was progressive from this time.

On admission to Robroyston Hospital on 18.10.48, the patient was found to be six months pregnant. The disease now affected both lungs extensively, and she had also developed tuberculosis of the left hip joint.

Ten days after admission she had a miscarriage, and subsequently her general condition seemed to improve a little, but this was short lived. Cyanosis and dyspnoea were marked features, and the temperature was remittent. The pain in the hip necessitated traction and Morphine analgesia.

Oxygen was administered at intervals during the last week of life, and had some interesting effects on the blood chemistry.

The Xray report on 21.10.48 was that there was an extensive bronchopneumonia lesion throughout both lungs.

24 hours before death, the patient lapsed into coma; the

breathing gradually became shallower and ultimately irregular and gasping.

Blood was withdrawn by cardiac puncture within 5 minutes of death.

Diagnosis : Pulmonary Tuberculosis.

Case 35. A.C. Female. Age 20. Admitted : 4.2.48
Died : 24.11.48

The patient was a known tuberculous subject since April 1946. She had been nursed in the Southern General Hospital from April to December 1946, and on discharge attended a Tuberculosis Clinic for "refills" of a right artificial pneumothorax. The latter was abandoned in July 1947.

She had a haemoptysis in December 1947, which did not recur, but her general condition grew worse, and she was admitted to Robroyston Hospital on 4.2.48.

Xray of chest at this time showed that there was a tuberculous consolidation throughout both lungs, with pleural thickening. There was a small effusion at the right base and large cavities in the left lung.

Serial Xrays confirmed the clinical assessment that the disease was active and progressvive.

The patient received the usual conservative and Sanatorium regime - strict bed rest, fresh air and nutritious feeding, but the course of her illness was steadily downhill. It was noted that the deterioration was hastened with the advent of Winter.

When the first blood estimation was done, the patient was only moderately cyanosed and her respirations were a little hurried. She steadily became more dyspnoeic and toxic, and her parents took her home against advice on 22.11.48; it was learned that she died two days later, on 24.11.48.

The last blood estimation was done on 21.11.48, three days before death.

Diagnosis : Pulmonary Tuberculosis.

Case 36. R.E. Male. Age 36. Admitted : 21.7.48
Died : 23.11.48

Pulmonary tuberculosis had been diagnosed in the case of this patient in 1942, and he was admitted to a Sanatorium from 1943 until 1944. He remained fairly well after that until December 1947 when he lost weight and developed pain in both thighs. He had developed tuberculosis of the lumbar spine.

He was admitted to Robroyston Hospital on 21.7.48 in a poor condition. He was thin and toxic looking.

Xray of spine revealed severe tuberculous caries of L. 1 and 2, with almost complete destruction of L.2. There was productive disease throughout both lungs with cavitation in the left upper half.

Whilst in hospital, the patient's general condition did not improve, and he had several small haemoptyses. A pneumo-peritoneum was induced, and this seemed to have some affect in controlling the bleeding. There was no paraplegia or bladder upset, although the patient continued to complain of pain in both thighs.

About a week before death, when the first estimations were done the patient was cyanosed and had developed a little oedema of the ankles and sacral pad. The breathing was quiet.

Rapid deterioration followed, and when the last specimen was withdrawn 1½ hours before death, he was semi-comatose, and the breathing was irregular and shallow.

His temperature had been high for several weeks.

Morphine had been administered as required during the last week of life.

Diagnosis : Pulmonary Tuberculosis.

Case 37. M.G. Female. Age 32. Admitted : 7.11.48
Died : 7.12.48

The patient was admitted to the Sanatorium from the Maternity Unit of Robroyston Hospital on 7.11.48. She was 5½ months pregnant, and was suffering from advanced bilateral pulmonary tuberculosis.

Her general condition was very poor; the temperature showed an average swing from 100° to 97° and there was a constant

tachycardia.

She had lost a lot of weight, and the face was flushed and she complained of severe night sweats.

Her chest condition was aggravated by a severe and painful tuberculous laryngitis which necessitated regular Morphine and semi-solid food.

Progress. There was no improvement with bed rest and she steadily deteriorated. The cough was distressing, and sputum abundant.

When the first blood estimation was done there was no obvious dyspnoea at rest.

Two days before death the breathing became somewhat laboured and the patient was restless. This gradually changed in the next 48 hours to the shallow, rapid type of respiration, which, as death approached, became irregular and gasping. She died at 5.45 a.m. on 7.12.48, and blood was immediately obtained by cardiac puncture. Morphine was the only drug administered.

Diagnosis : Tuberculous Laryngitis.
Pulmonary Tuberculosis.

Case 38. C.G. Female. Age 24. Admitted : 21.10.47.
Died : 28.11.48.

This patient was originally admitted to the pneumonia ward of Robroyston Hospital as a case of acute pneumonia. When the diagnosis of pulmonary tuberculosis was made, she was transferred to the Sanatorium.

A left artificial pneumothorax was induced on 12.11.47, but a hydropneumothorax developed. This was repeatedly aspirated, and later the artificial pneumothorax was abandoned when it was discovered that the disease had spread to the right midzone.

From June to September 1948 she received a course of Para-amino-Salicylic acid, 23 grams per day, which was then on clinical trial. There was no clinical or radiological improvement: rather the reverse.

On 13.10.48 Xray of chest showed spreading disease in the right lung with cavitation in the second interspace. There was a large hydropneumothorax in the left side.

The patient gradually deteriorated, and during the last two days of life when the biochemical estimations were being done, the patient was pale, cyanotic and emaciated.

No great dyspnoea was noted until the 48 hours before death when breathing was seen to be difficult. As the patient passed from semi-coma to deeper coma, the respirations became more shallow, ultimately changing to the slow irregular gasps seen in the immediate pre-agonal period.

Pyrexia had been present for many months, falling to subnormal 24 hours before death.

Blood was obtained by cardiac puncture immediately after death.

Diagnosis : Pulmonary Tuberculosis.

Case 39. M.McC. Female. Age 25. Admitted : 22.7.48.
Died : 15.12.48.

In March 1948 the patient developed a bad cold with a cough which persisted longer than expected. She began to get easily tired and felt listless. On being referred to a Tuberculosis Clinic, her sputum was found to be positive for tubercle bacilli.

She was admitted to Robroyston Hospital on 22.7.48 and her general condition was seen to be poor. She was pale and toxic looking and had lost some weight. Cough was troublesome, and her sputum abundant. There was no dyspnoea at rest.

Xray of chest on 5.8.48 revealed extensive, active tuberculosis in the right and left upper two thirds, and there was a large cavity in the left upper half.

Progress There was a persistent low grade pyrexia and a fast pulse, and weight was gradually lost despite careful conservative measures.

On 9.8.48 a course of 23 grams Para-amino-Salicylic acid per day was commenced, but on 29.8.48 toxic symptoms of the drug appeared (which had been noted in several other patients receiving the "acid" form of the drug), namely extrasystoles,

oedema, and peripheral neuritis. The Para-amino-Salicylic acid was discontinued.

The general condition rapidly deteriorated, and on 30.11.48, dyspnoea ar rest was evident.

By 6.12.48 Morphine had to be administered to keep the patient comfortable.

14.12.48. Patient comatose; respiration hurried (35 per minute) and shallow. There was leaden hue of the lips.

15.12.48. The patient died at 11.35 a.m.

The temperature had dropped to a subnormal level within the last 24 hours.

Blood was removed by cardiac puncture within 10 minutes of death.

Diagnosis:
Pulmonary Tuberculosis.

Case 40. J.H. Female. Age 22 Admitted : 9.12.48
Died : 24.12.48

This patient was admitted to the Sanatorium on 9.12.48 from the Obstetric Unit where she had had a hysterotomy and sterilisation performed. This had been advised because of severe pulmonary tuberculosis.

Her general condition was extremely poor on admission, and no Xray of the chest was done on account of her advanced cachexia, and because a record of her most recent chest Xray was obtained from the Out-Patient Dispensary.

This showed extensive, active tuberculosis, most marked in both upper thirds, with spreading infiltration towards both bases. The sputum contained abundant acid-alcohol-fast bacilli.

The patient was pale, thin and toxic looking, and showed the typical malar flush and prominent cheeckbones through loss of flesh. Night sweating was profuse and the temperature ranged from 99° to 101° with tachycardia.

The first blood estimation was done when the patient was only slightly dyspnoeic, but from then onwards her general condition steadily deteriorated and dyspnoea at rest became more marked.

About 24 hours before death the patient lapsed into a semi-comatose condition, but could be roused. The respirations became shallow and fast, ultimately becoming slow and irregular two hours before death.

Blood was obtained by cardiac puncture within 10 minutes after death. Drugs administered during the last 6 days were Nembutal and Morphine.

Diagnosis : Pulmonary Tuberculosis.

Case 41. J.D. Female. Age 22. Admitted : 15.12.48
Died : 11. 1.49

This girl had been attending a Tuberculosis Clinic in March 1947 and at that time was known to have tuberculous infiltration in both upper thirds of the lungs. She was also pregnant, but she miscarried.

Following the miscarriage, her health had become worse although she carried on her household duties.

When seen at her Tuberculosis Clinic on 10.5.48 it was found that she was again pregnant. She was ill-looking, had a bad cough and spit, and had lost several pounds in weight since her last attendance at the Clinic.

The chest signs were of very active bilateral disease.

The patient was brought to hospital on 15.12.48 because she was almost at term, and a live child was subsequently born on 19.12.48.

Before the confinement her temperature had been settled, but immediately afterwards it began to rise and swing. The general condition began to deteriorate rapidly, but dyspnoea at rest was not noticeable until the actual day of death when she became semi-comatose and the respirations became laboured and difficult. During the last hour of life the respirations were slow, noisy and shallow.

Morphine had been given for only 36 hours before death.

Diagnosis : Pulmonary Tuberculosis.

Case 42. M.S. Female. Age 36. Admitted : 8.1.49
Died : 8.1.49

The patient was admitted to the acute pneumonia ward of Robroyston Hospital at 4 p.m. on 8.1.49 in a moribund state.

She gave a history of having attended a Tuberculosis Clinic two years previously because of a "shadow" in one lung which was suspected to be tuberculous in nature. After various investigations she was told that the condition was probably not tuberculous, and consequently she never bothered to attend the Clinic again.

The present illness dated back many months, the presenting complaints being cough, dyspnoea, night sweats and loss of weight.

On examination, the patient was thin and cahectic, and the skin was drenched in perspiration.

Clinically there was extensive involvement of both lungs with marked dulness to percussion on the right side with fine creps all over both lung fields. There was presumably very little healthy lung tissue remaining.

After the patient had been out to bed, dyspnoea gradually became worse, and the rapid respirations changed to the slower, shallow type usually seen in the pre-agonal period.

The patient died at 10.55 p.m.

She had received no drug treatment. The temperature, which was 102° on admission fell to subnormal just before death.

Blood was obtained by cardiac puncture immediately after death.

No post mortem was performed.

Diagnosis : Pulmonary Tuberculosis.

Case 43. T.W. Male. Age 36. Admitted : 10.1.48
Died : 27.1.49

The patient first complained of a cough which did not clear up, in April 1947. The sputum became profuse after a few weeks and he had gradually increasing dyspnoea on exertion. Ultimately, his doctor send him for an Xray of chest in

October 1947, which confirmed the presence of pulmonary tuberculosis.

He was admitted to Robroyston Hospital on 10.1.48, his general condition being only fair, He was slightly cyanosed and had a bad cough with an abundant purulent sputum which contained numerous acid-alcohol-fast bacilli.

On 2.7.48 the Xray report was "There is tuberculous disease throughout both lungs, and on the right side cavitation is multiple and extends from apex to base".

The report 5 months later on 12.11.48 was that the cavitation had greatly increased on both sides.

On 15.12.48 the patient, who previously had maintained a fair degree of health, had a copious haemoptysis which left him very breathless and orthopnoeic, but did not seem to alter his condition very much. He remained static for another three weeks until 17.1.49 when the breathlessness became extreme necessitating Morphine. He remained in this distressed condition under the influence of Morphine for the next 10 days until death.

Respirations on the last 3 days of life were very slow, shallow and noisy, and the patient became semi-comatose. The temperature was subnormal for the last 8 days.

Blood was withdrawn by cardiac puncture immediately after death.

Diagnosis : Pulmonary Tuberculosis.

Case 44. A.G. Male. Age 19. Admitted : 8.1.48
Died : 11.2.49

After having a refill of a right artificial pneumothorax at a Tuberculosis Clinic, the patient felt unwell and had a brisk haemoptysis.

He was admitted to Robroyston Hospital on 8.1.48 in a toxic condition, with a temperature reaching 102° and the pulse ranging from 100 to 120. The right artificial pneumothorax was abandoned.

The Xray report on the chest on 28.1.48 was "Each lung shows bronchopneumonic tuberculosis; the right upper lobe is blacked out in its lower half and the apex is adherent".

After a period of bed rest and Sanatorium regime, the patient settled down and eventually the temperature became normal, although the pulse rate remained high.

A left artificial pneumothorax was induced, but after several weeks a hydropneumothorax developed, and it was abandoned.

By the beginning of December 1948, the patient's general condition was showing signs of deterioration, having remained fairly stationary for several months. He was pale, rather thin, but showed no sign of dyspnoea at rest. His ankles were swollen and there was a moderate ascites.

During December 1948 and January 1949, the general condition deteriorated further; the ascites increased to a degree necessitating repeated aspirations for the comfort of the patient. Diarrhoea was troublesome and was only partially controlled by Tinct. Opii.

On 31.1.49 when the second blood sample was taken, the patient was slightly dyspnoeic at rest. The temperature was remittent to 100°, and oedema of ankles, ascites and diarrhoea were marked.

He gradually became weaker and three days before death lapsed into semi-coma, dyspnoea now becoming a feature.

He died on 11.2.49.

Diagnosis : Pulmonary Tuberculosis.
Tuberculous enteritis.

Case 45. E.K. Female. Age 50. Admitted : 25.1.48
Died : 29.1.48.

Whilst shopping on 24.1.48, the patient collapsed and was brought to Glasgow Royal Infirmary in a semi-conscious state.

As far as was known, the patient had been in good health previously.

Examination revealed loss of power of the left side of face, left arm and leg. The speech was noticeably affected, and she could only reply disjointedly in monosyllables to questions.

The breathing was noisy, about 25 per minute, but regular. The heart was found to be enlarged; the apex being palpable 5" to the left of the midsternal line in the 5th interspace. The blood pressure was 165/90. There was a faint trace of albumin in the urine. The radial arteries were tortuous and hard.

On 27.1.48 the condition of the patient was about the same as on admission, but 24 hours later she became comatose and the breathing became Cheyne-Stokes in type. She died on 29.1.48.

Diagnosis : Cerebral Haemorrhage.

Case 46. M.A. Female. Age 17. Admitted : 12.4.48.
Died : 13.9.48.

The patient was admitted to Robroyston Hospital on 12.4.48 after developing a right spontaneous pneumothorax.

Apart from the development of a hydropneumothroax, the patient began to make a steady recovery.

Xray of the chest on 26.5.48 confirmed the presence of a hydropneumothorax, but also revealed tuberculous infiltration in the upper third of the left side.

The chest was aspirated on numerous occasions, but after the last aspiration on 10.8.48, the temperature began to rise and remained continuous.

She became irritable and nuchal rigidity became obvious on 1.9.48. Her condition rapidly deteriorated and it was clear that she had developed tuberculous meningitis. Morphine was administered on 10.9.48 and by 13.9.48 the respirations had become slow and of the Biot type. She died at 8 p.m. on the same day.

Blood was removed by cardiac puncture immediately after death.

Diagnosis : Pulmonary Tuberculosis.
Tuberculous Meningitis.

Case 47. B.M. Female. Age 22. Admitted : 18.10.48
Died : 5.11.48

This patient gave a history of cough, spit, amenorrhoea and night sweats of about 3 month's duration.

She had lost weight and was anaemic, and the general condition was poor.

The disease in the lung was confined to moderately active tuberculous infiltration in the upper third of the left lung, but the main cause of the present illness was due to tuberculous enteritis.

Deterioration was rapid, and diarrhoea was only poorly controlled by Tint. Opii. She was languid and pyrexia was high. Repirations were not particularly difficult, but on the day of death they became shallow and ultimately irregular about half-an-hour before death.

Diagnosis : Abdominal Tuberculosis.

Case 48. W.R. Male. Age 55. Admitted : 16.1.48
Died : 29.1.49

The patient had been in hospital for about 12 months. His condition had remained static for a long time, but in the last three months there had been noticeable deterioration.

He had extensive pulmonary tuberculosis and eventually developed oedema of the ankles and ascites.

He gradually became comatose and died on 29.1.49.

Blood was withdrawn by cardiac puncture five minutes after death.

Diagnosis : Pulmonary Tuberculosis.

Case 49. H.L. Male. Age 47. Admitted : 5. 6.46
Died : 27.11.48

Pulmonary tuberculosis had been diagnosed a year previous to admission on 5.6.46.

During the first year of his stay in hospital, there had been some improvement in his condition and the weight had increased by one stone, but thereafter he began to lose ground steadily.

Serial Xrays of chest revealed that the disease was gradually spreading.

One month before death, the patient was confined strictly to bed again because the temperature had begun to rise above the normal. He was not particularly dyspnoeic at rest.

On 16.11.48 the bowels became loose and he complained of distressing abdominal colic, signifying tuberculous ulceration of the intestine. This was controlled by regular administration of Tinct. Opii.

It was obvious, however, that death would not be long delayed, and on 26.11.48 he became comatose and the breathing became shallow and increased in rate. During the early hours of 27.11.48 the respirations became irregular and gasping, and death occurred at 2.5 a.m.

Diagnosis : Pulmonary Tuberculosis.
Tuberculous Enteritis.

Case 50. D.W. Male. Age 31. Admitted : 21.4.47
Died : 5.11.48

The patient had been ill at home since December 1946, and when admitted to Robroyston Hospital on 21.4.47 he was found to be an advanced case of pulmonary tuberculosis.

His sputum was positive for acid-alcohol-fast bacilli up to the time of death.

He developed a right empyema which was repeatedly aspirated, and ultimately required a rib resection on 3.8.48. The wound became septic, broke down, and thereafter his condition rapidly deteriorated.

Terminally the temperature became hectic, and the pulse high. Dyspnoea became marked three days before death, and he ultimately became comatose and died on 5.11.48.

Diagnosis : Pulmonary Tuberculosis.

(d) Cases A, B and C.

Three cases were studied, two of congestive cardiac failure with recovery, and the third of chronic renal failure with uraemia who died.

These cases are presented for comparison with those of the main series.

Case A. M.C. Female. Age 34. Admitted : 1.11.48

The patient gave a history of "heart trouble" for the past 13 years, and on admission to Robroyston Hospital she was acutely ill, dyspnoeic and cyanosed. There was massive oedema of the legs and sacral pad, and the jugular veins were grossly congested. The skin was noticeably icteric.

Examination of the cardiovascular system revealed that the pulse was irregular, 145 per minute, and the apex beat was palpable 5 inches to the left of the midsternal line in the 5th interspace. There was a presystolic thrill and murmur, and a rumbling mid-diastolic sound at the apex. The liver was palpable 4 inches below the right costal margin.

Progress The first blood and urine samples were taken on the day after admission.

After a week, the patient began to show signs of improvement with rest and digitalisation, and thereafter improvement was steady. By the 20th December 1948 there was no dyspnoea or oedema, and she was discharged.

Diagnosis . : Mitral Stenosis.
Congestive Cardiac Failure.

Case A.

Date	Nov.48 2nd	7th	14th	Dec.48 18th				
Number of days before death	-	-	-	-				
" " hours " "	-	-	-	-				
Plasma Bilirubin mgms.%	5.9	4.3	3.2	1.4				
Plasma Bicarbonate mgms.%	39.2	-	48.0	53.6				
Hb.% (100% ≡ 14 g.%)	84.0	81.0	92.0	96.0				
Venous 0_2 Sat. CCS/100 CCS.	2.1	3.2	4.4	10.5				
Plasma Chlorides mgms.%	543.0	554.0	562.0	598.0				
Plasma Phosphorus mgms%	5.8	3.2	2.7	2.2				
Blood Lactic Acid. mgms.%	44.0	31.0	18.0	10.0				
Blood Urea. mgms.%	75.0	70.0	60.0	30.0				
Serum Calcium mgms.%								
Plasma Proteins g.%								
URINE.								
pH.	5.1	5.7	7.5	6.7				
Ammonia. Vols. N/10 %.								
Tit.Acidity Vols. N/10 %.								
Chlorides grammes/litre.	2.2	4.3	5.66	6.32				

Case B. J.R. Female Age 54. Admitted : 24.2.47

The patient was admitted to Glasgow Royal Infirmary with severe congestive cardiac failure. She was grossly oedematous and there was ascites.

Examination showed an irregular fast pulse and well marked venous congestion. The heart was enlarged and there was a rumbling presystolic murmur at the apex.

The patient's condition remained grave for many weeks and despite digitalisation and mercurial diuretics, the ascites and oedema persisted. However, eventually the oedema began to subside after prolonged bed rest and there was no trace of it by 7.7.48. Dyspnoea had also disappeared.

She was allowed to go home much improved on 15.7.48.

Diagnosis : Mitral Stenosis.
Congestive Cardiac Failure.

Case B.

Date	May 48 4th	July 48 9th						
Number of days before death	-	-						
" " hours " "	-	-						
Plasma Bilirubin mgms.%	3.85	0.93						
Plasma Bicarbonate mgms.%	44.3	52.4						
Hb.% (100% ≡ 14 g.%)								
Venous 0_2 Sat. CCS/100 CCS.								
Plasma Chlorides mgms.%	556.0	583.0						
Plasma Phosphorus mgms%	4.9	2.25						
Blood Lactic Acid. mgms.%								
Blood Urea. mgms.%								
Serum Calcium mgms.%	9.6	9.3						
Plasma Proteins g.%	5.6	6.4						
URINE.								
pH.	5.2	6.9						
Ammonia. Vols. N/10 %.	98.4	54.8						
Tit.Acidity Vols. N/10 %.	106.2	40.4						
Chlorides grammes/litre.	1.92	6.3						

Case C. T.H. Male. Age 32. Admitted : 28.12.47
Died : 30.12.47

The patient was admitted to Glasgow Royal Infirmary with a history from relatives of having had a sore throat three weeks before admission, followed by a skin eruption, anorexia, sleeplessness and convulsions.

He was comatose, and the muscles of the arms, legs and face were twitching. The breathing was of "hissing" character.

There was a previous history of recurrent "kidney trouble" since 1937.

The urine had a specific gravity of 1.007, contained a thick cloud of albumin, and microscopically granular casts and red blood cells were seen. The blood pressure was 200/110.

The patient did not recover consciousness and died two days after admission. Although no autopsy was carried out, the diagnosis was considered to be clearly one of uraemia consequent on chronic nephritis.

The specimen of blood examined was obtained by venepuncture 15 minutes before death, and the urine was obtained by catheterisation immediately after death.

Diagnosis : Uraemia
Chronic Nephritis.

Case C.

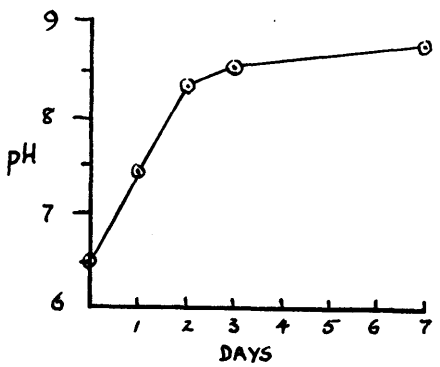
Date	Decr. 47 30th							
Number of days before death " " hours " "	- $\frac{1}{4}$							
Plasma Bilirubin mgms.%	2.1							
Plasma Bicarbonate mgms.%	10.0							
Hb.% (100% ≡ 14 g.%)								
Venous 0_2 Sat. CCS/100 CCS.								
Plasma Chlorides mgms.%	676.0							
Plasma Phosphorus mgms%	8.4							
Blood Lactic Acid. mgms.%								
Blood Urea. mgms.%	356.0							
Serum Calcium mgms.%								
Plasma Proteins g.%								
URINE.								
pH.	4.4							
Ammonia. Vols. N/10 %.								
Tit.Acidity Vols. N/10 %.								
Chlorides grammes/litre.	0.13							

Appendix (e) Preservation of Urine and the pH.

Several experiments were performed to demonstrate the changes of pH which take place in urine which is allowed to stand both preserved with toluol, and unpreserved. These are presented below in tabular and graphic form.

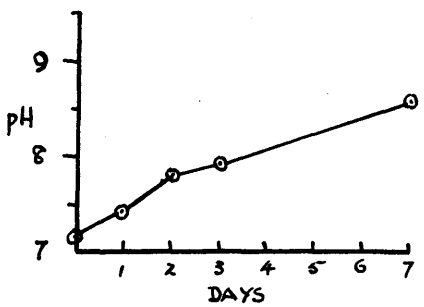
Experiment 1. J.L. Urine unpreserved.

13.5.47 pH 6.5
14.5.47 pH 7.4
15.5.47 pH 8.3
16.5.47 pH 8.5
20.5.47 pH 8.7



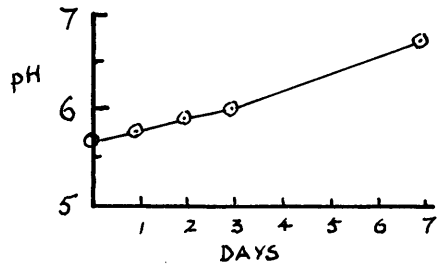
Experiment 2. J.C. Urine unpreserved.

13.5.47 pH 7.2
14.5.47 pH 7.4
15.5.47 pH 7.8
16.5.47 pH 7.9
20.5.47 pH 8.6



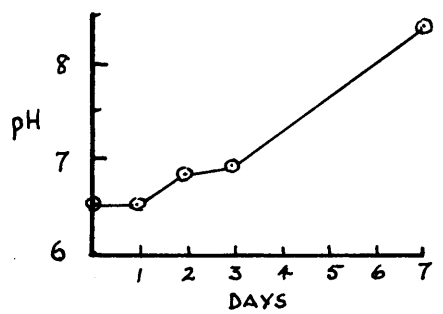
Experiment 3. J.Mc. Urine unpreserved.

13.5.47 pH 5.7
14.5.47 pH 5.8
15.5.47 pH 5.9
16.5.47 pH 6.0
20.5.47 pH 6.8



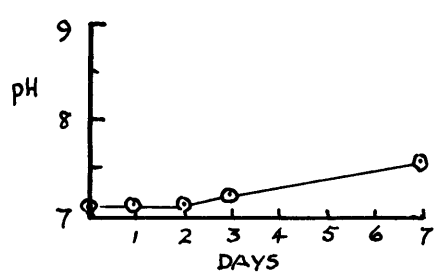
Experiment 4. H.K. Urine unpreserved.

13.5.47 pH 6.5
14.5.47 pH 6.5
15.5.47 pH 6.8
16.5.47 pH 6.9
20.5.47 pH 8.4



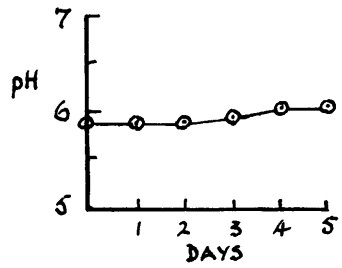
Experiment 5. A.R. Urine preserved with Toluol.

13.5.47 pH 7.1
14.5.47 pH 7.1
15.5.47 pH 7.1
16.5.47 pH 7.2
20.5.47 pH 7.6



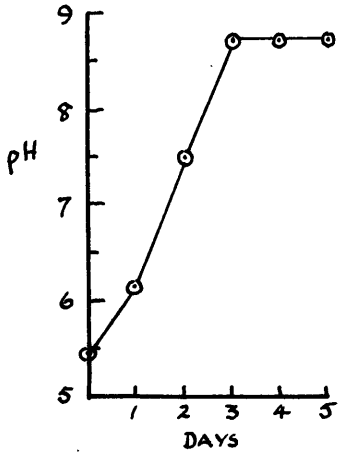
Experiment 6. A.P. Urine preserved with Toluol.

22.5.47 pH 5.8
23.5.47 pH 5.8
24.5.47 pH 5.8
25.5.47 pH 5.9
26.5.47 pH 6.1
27.5.47 pH 6.1



Experiment 7. J.J. Urine unpreserved.

27.6.47 pH 5.4
28.6.47 pH 6.2
29.6.47 pH 7.5
30.6.47 pH 8.7
1.7.47 pH 8.7
2.7.47 pH 8.7



These experiments show that the pH of unpreserved urine rises rapidly from day to day if left standing. The rate of rise is dependent on the bacterial content particularly of those organisms splitting urea to form ammonia.

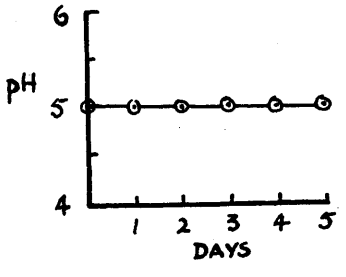
A specimen of urine was boiled in order to kill any bacteria, and the pH estimated daily for six days. This remained the same throughout. (See Experiment 8.)

The preserved urine was noted to maintain the same pH for about three days. after which there tended to be a slight rise.

It is important therefore that urine for examination of pH and ammonia content should be preserved, and even then it should preferably be tested within 24 hours of collection.

Experiment 8. Urine Boiled

3.7.47 pH 5.0
4.7.47 pH 5.0
5.7.47 pH 5.0
6.7.47 pH 5.0
7.7.47 pH 5.0
8.7.47 pH 5.0



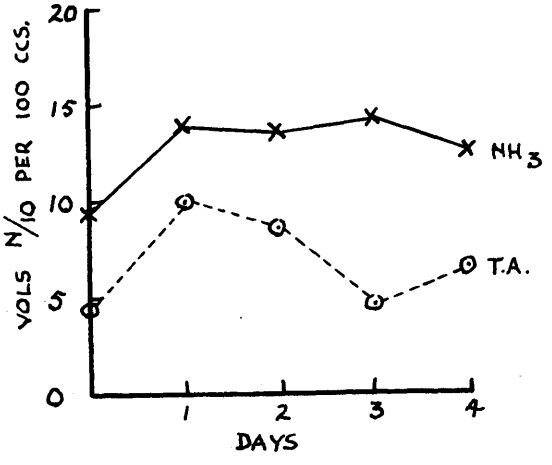
Appendix (f) Normal Ammonia Excretion.

An experiment was performed to show the normal ammonia and titrable acid excretion in the urine from day to day.

A patient, T.H., who had been admitted to the Medical Wards six weeks previously suffering from an attack of acute bronchitis was convalescing. He had not shown any

symptoms for two weeks and was on a normal hospital diet. The estimations were performed on 24 hour specimens of urine preserved with Toluol.

N/10 per 100 c.cs.	Titratable Acidity.	Ammonia.
1.3.47	4.8	9.6
2.3.47	10.0	14.0
3.3.47	8.8	13.6
4.3.47	4.8	14.4
5.3.47	6.6	12.8



Appendix (g) The effect of ingestion of 10 grammes of Sodium Bicarbonate

The effect of taking 10 grammes of Sodium Bicarbonate by mouth was demonstrated in a normal healthy subject M.B.

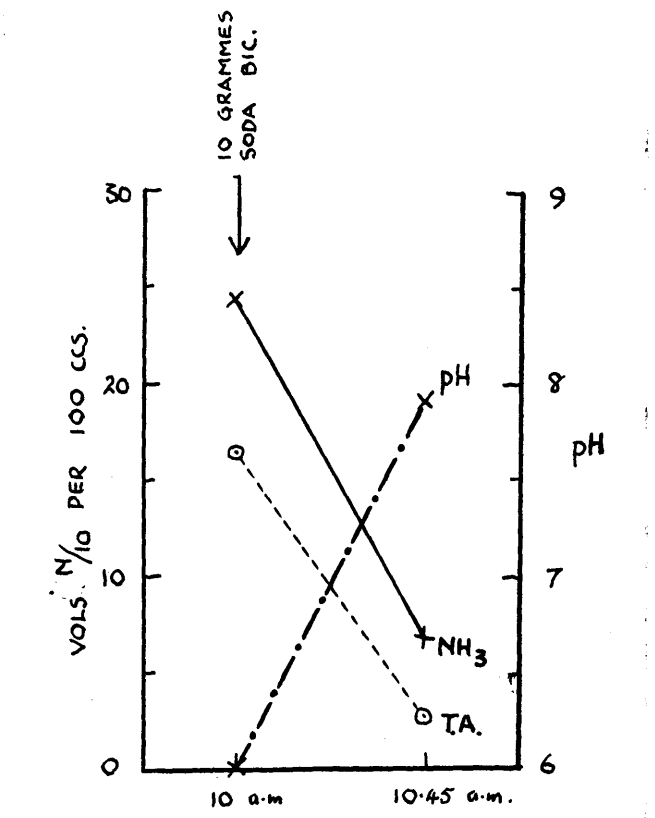
The bladder was emptied at 10 a.m. 11.7.47, and estimations of urinary pH, Titratable acidity and ammonia were performed. Blood was also taken by venepuncture and the plasma bicarbonate and plasma chloride estimated.

The subject swallowed 10 grammes of Sodium Bicarbonate dissolved in water and rested until 10.45 a.m. when the bladder was again emptied and blood taken.

The tabulated results are shown as follows : -

	Urine	Blood
10 a.m.	pH = 6.0	Plasma
	Titratable	Bicarbonate = 58.6 vols.%
	Acidity = 16.4 vols.n/10%	Plasma
	Ammonia = 24.4 vols.n/10%	Chloride =569.0 mgm.%
	10 grammes Sodium Bicarbonate swallowed.	
10.45 a.m.	pH = 7.9	Plasma
	Titratable	Bicarbonate = 60.4 vols.%
	Acidity = 2.8 vols.n/10%	Plasma
	Ammonia = 6.8 vols.n/10%	Chloride =604.0 mgms.%

In graphic form the urine results are as follows : -



The changes in the blood were found to be neglible, and therefore not worth recording graphically.

The amount of alkali given produced a marked fall in ammonia and titratable acid excretion and a reciprocal rise in the pH of the urine.

No great change was found in the plasma bicarbonate or chloride due to efficient buffering of the blood.

Appendix (h) Methods

1. Plasma Bicarbonate. Titration Method of Van Slyke (1922). This method involves the estimation of the bicarbonate content of the plasma under conditions of normal alveolar CO_2 tension.

The blood was collected under liquid paraffin in a heparinised tube, centrifuged immediately and the plasma separated.

2. Plasma Inorganic Phosphorus. Method of Briggs (1922). The principle of the method is, the proteins are precipitated with trichloracetic acid. An aliquot portion of the filtrate is treated with molybdic acid and the phospho-molybdic acid thus formed is reduced to a blue coloured compound by hydroquinone plus sodium sulphite.

Since hydrolysis of the glycerphosphates into glycerol and inorganic phosphate by phosphatase takes place readily in blood allowed to stand for long, the specimen was centrifuged immediately and the proteins precipitated from the plasma.

3. Plasma and Urinary Chlorides. Method of Van Slyke and Sendroy (1923).

Principle. The proteins are destroyed and the chlorides are precipitated as silver chloride by heating with concentrated nitric acid and a known amount of silver nitrate.

Excess of silver nitrate is determined by titration with potassium thiocyanate using iron alum as an indicator.

4. Bilirubin in Plasma. Method of Van den Bergh modified by McNee and Keefer (1925)

5. Blood Lactic Acid. Method of Barker and Summerson (1941) The principle of the method is that the glucose and other interfering substances are removed from the protein free blood filtrate by the Van Slyke-Salkowski method of treatment with copper sulphate and calcium hydroxide. An aliquot of the resulting solution is heated with concentrated sulphuric acid to convert lactic acid to acetaldehyde, which is then determined colorimetically by reaction with p-hydroxydiphenyl in the presence of copper ions.

In the original description a photo-electric colorimeter was used but since this instrument was not available to the author, a Klett-Bio colorimeter was used instead.

6. Blood Urea. Method of Archer and Robb (1925)
The final colour was matched with Lovibond Comparator Discs, and the result expressed to the nearest 5 mgms.

7. Oxygen content of blood. Method of Haldane (1920)
The estimations were performed with Haldane's apparatus constructed from the original by Dr. G.J. Aitken and kindly loaned to the author.

8. Serum Calcium. Clark-Collip modification of the Kramer-Tisdall Method (1925)

9. Plasma Proteins. Gravimetric method of Phillips, Van Slyke, Dole, Emerson, Hamilton and Archibald (1945).
The copper sulphate solutions were prepared under the personal supervision of the author in the Laboratory attached to Ward 4. Glasgow Royal Infirmary.

10. pH of Urine. Capillator Method (B.D.H.)

11. Ammonia in Urine. Formol titration method after Cole (1941)
This method estimates both ammonia and amino acids and is therefore only an approximate measure of the amount of ammonia in urine.

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