ELECTROCARDIOGRAPHY IN IDIOPATHIC HYPERCALCAEMIA

AND OTHER CATION DISORDERS OF CHILDHOOD

By

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A Thesis

submitted for the degree of M.D.

UNIVERSITY OF GLASGOW

March 1961

ProQuest Number: 13855601

ProQuest 13855601

C O N T E N T S

P R E F A C E

Those privileged to practise clinical medicine are constantly reminded of their growing debt to the enterprise of the biochemist. The careful evaluation of symptoms and clinical signs remains supremely important but the physician may often find it advantageous to call upon the resources of the laboratory not only to ensure more precise diagnosis and the most effective treatment, but also to gain a clearer understanding of morbid processes. No department of medical practice can have derived greater benefit from biochemical research than that which is concerned with the diseases of children, and here the knowledge which has been gained of the inorganic fabric of the body, and of the electrolytes in particular, has wide applications.

My investigations received their stimulus from the frequency of electrolyte disorders in early childhood, but I have confined my attention to disorders of cation balance, and in these to a study of electrocardiography as a diagnostic procedure. I have made electrocardiographic examinations of children suffering from hypercalcaemia, hypocalcaemia, hyper-kalaemia, hypokalaemia and hypernatraemia, but particular atten-tion has been paid to the electrocardiographic signs of idiopathic hypercalcaemia of infancy. In order that standard measurements might be available for comparison, electrocardiograms of healthy infants/

infants were recorded and analysed. These electrocardiographic studies are based on 227 examinations of 147 children. A possible interpretation of the electrocardiographic signs of idiopathic hypercalcaemia led me to investigate in the rabbit the effect of vitamin D on the heart. In this experiment which was of modest proportions 27 rabbits were studied; the results are based on the examination of 640 tissue sections.

My interest in problems concerned with electrolyte balance was inspired by Professor Stanley Graham; for this and for his constant encouragement and unstinted advice I am deeply grateful. The patients whom I studied were under his care in the wards of the Royal Hospital for Sick Children, Glasgow.

I express my thanks to Dr. H.E.C. Wilson and to Dr. M. Sonja McBean for permission to quote so freely the results of determinations made in the department of biochemistry at the Royal Hospital for Sick Children, Glasgow. It is a pleasure to express my gratitude to Dr. A.M. MacDonald for his generous advice, and for putting at my disposal the resources of the department of pathology at this hospital. I am indebted to Dr. Margaret D. Giles for permission to examine infants under her care at the Child Welfare Clinic at the Royal Hospital for Sick Children. I gratefully acknowledge the invaluable assistance and/

That part of my investigations which concerns the electro-
cardiographic features of idiopathic hypercalcaemia of infancy,
but without the statistical analysis of the results, has been
published in the British Medical Journal (Brit. Med. J. (1959)
2. 467). The analysis of time intervals in electrocardiograms
of healthy infants which forms the first part of these investi-
gations is shortly to be published in the Acta Paediatrica.

THE BIOCHEMICAL BACKGROUND

T H E   B I O C H E M I C A L   B A C K G R O U N D

The wide distribution of calcium, potassium and sodium throughout the body testifies to their equally wide range of physiological activity.   In the extracellular fluid the concentration of cations provided by these metals and by magnesium is maintained and kept in equilibrium with the concentration of anions through the harmonious operation of an array of inter-dependent mechanisms.   Should any of these fail, a profound disturbance of ionic balance may ensue with important changes in the concentration of cations in the extracellular and even in the intracellular fluid.   Many physiological processes depend upon the separate and specific actions of calcium, potassium or sodium, and the concentration of each metal must therefore be maintained within narrow limits, or grave impairment of health may result.

Fifty years ago scarcely anything was known of the relation-ship between inorganic substances and disease.   Research had begun in the nineteenth century but progress had been slow because the available methods for chemical analysis were unsuited to clinical investigation.   Yet even at that time the idea of balance as a cardinal feature of physiology was not new.   As early as 1614 Sanctorius of Padua had postulated not only the existence of a balance between retention and excretion regulated by a deficit or excess/

excess within the body, but also the importance of this balance to the maintenance of health. In De Statica Medicina he enunciated this principle in simple terms: "Si quanta et qualis oporteat, quotidie fieret additio eorum quae deficiunt, et ablatio eorum quae excedunt, sanitas amissa recuperaretur et praesens semper conservaretur."

It was not until 1736 that sodium was recognized to be a separate chemical substance, and not until the opening of the nineteenth century that sodium, calcium and potassium were isolated.

THE NINETEENTH CENTURY

One of the earliest studies of these metals was made by Justus von Liebig, Professor of Physiology at the German University of Giessen, who in 1842 published a treatise entitled "Animal Chemistry or Organic Chemistry in its application to Physiology and Pathology". This work addressed to the British Association for the Advancement of Science arose from a study of vegetable and animal chemistry prepared for the Association at its meeting in Glasgow in 1840. Liebig detected common salt in blood, bile and urine. He was of the opinion that it was required for the formation of blood and bile, and that it was excreted in the urine after having been used for vital processes or when ingested in/

in excess of physiological requirements. He concluded that common salt was "beyond all doubt" necessary for organic processes. He found potassium in bile and stated that this metal was required for the production of milk.

Eight years later Carl Schmidt (1850) published an account of his investigations into the chemical composition of the blood cells, plasma and serum of seven adults who were victims of an outbreak of cholera in Latvia during 1848. By way of introduction he reported an examination of two patients who were not suffering from cholera but who were subjected to therapeutic venesection for other reasons. He began by rejecting on theoretical grounds a current contention that the intracellular and extracellular fluids were of uniform composition. "Wasser gegen Wasser, Salzlösung gegen Salzlösung gleicher Concentration kann keinen Diffusionstrom veranlassen." ("There can be no cause for diffusion between water and water, and between salt solutions of equal concentration."). He proved this by showing that the concentration of sodium and calcium in the plasma was greater than in the cells and that the reverse was true of potassium. He demonstrated also that the plasma of patients with cholera was depleted of sodium and chloride. Further observations led him to indicate by implication the dependence of water balance upon osmotic tension; when salts were lost through the intestinal wall, transudation/

transudation of water kept pace until equilibrium was regained.

From Paris a few years later came the momentous work of Claude Bernard (1859, 1865). Bernard was concerned with the underlying purpose of the extracellular fluid. He described it as the milieu intérieur, the immediate environment of organs and tissues, as opposed to the milieu extérieur surrounding the periphery of the body. Upon its stable composition depended the integrity of the tissues. He was fully aware of the functions of the extracellular fluid in relation to homoeostasis and nutrition as is shown in this passage from a discourse on blood (1859):- " ...... in this environment ...... all tissues find unchanging conditions of temperature, humidity and oxygenation for the discharge of their functions, and, at the same time, nitrogenous, hydrocarbon and saline matter without which the organs cannot gain nourishment." He foresaw the exploration of the internal environment and, even more remarkable, he predicted the discovery therein of disorders which could cause disease.

Until the end of the century progress was slow, and many observations were concerned only with the corroboration of the findings of previous workers. Forster (1873) showed that animals died if sodium chloride was excluded from their diet. Wanach (1888) determined with considerable accuracy the amount of sodium and/

and potassium in the blood cells and serum of adults.   He confirmed

moreover that potassium was concentrated in the cells and sodium in

the serum, and Bunge in 1890 stated that potassium was an integral

and indispensable constituent of every cell.

The statement that a certain amount of calcium in plasma is

bound to protein was first made by Schmidt (1850) and later confirm-

ed by Pribram (1871).   This investigator used a method for the

estimation of calcium in serum which was to remain in use for over

forty years (McCrudden 1909-10).   The serum was reduced to ash in

a platinum crucible, the calcium in the ash was precipitated with

ammonium oxalate, the precipitate of calcium oxalate was converted

to calcium oxide by heating and the oxide was then weighed.

To provide enough blood or serum for chemical analysis required

a substantial venesection, and for the estimation of the salts of

metals the requirement was 100 to 200 millilitres of whole blood.

It was therefore impossible to study the chemistry of children in

health let alone in the course of disease.

A largely unhelpful method of analysis was introduced by Bunge

(1874) who reduced the bodies of young animals to ash and then

determined the mineral content.   Camerer and Söldner (1900ab) and

Steinitz (1904) later applied this method to infants who had died

soon after birth or in the course of nutritional disturbances.

Abderhalden (1906) admitted that the method could give insight

into/

into the inorganic composition of an organ but condemned its
inability to give a true picture of the manner in which the various
salts were distributed.

A method of investigation which was to prove of lasting value
in diagnosis and research was the metabolic balance study, the
quantitative comparison of output with intake. From Sanctorius
(1614) onwards, investigators had made measurements of excretions
and secretions, but in 1849, Barral, a Frenchman, stated that his
was the first attempt to compare output with intake. From studies
of his son and of three adults he calculated the difference between
the intake of metallic salts in food and their output in urine and
faeces. He defined the purpose of the balance study in these
terms: "Connaissant la quotité et la composition élémentaire des
aliments, tants solides que liquides, ingérés chaque jour, établir
la quotité et la composition élémentaire des évacuations, transpira-
tions et excrétions divèrses de manière à pouvoir poser l'équation
des gains et des pertes du corps humain."

One of the earliest applications of this technique was to the
investigation of the action of sodium chloride. In 1860 Voit
described balance studies of a dog whose diet was alternately
enriched with and depleted of this salt. Some of his conclusions
are no longer tenable, and in particular he declared that sodium
chloride/

chloride was a diuretic.   Using the same method for the study of
infants Freund (1898, 1904) set out to determine whether there could
be a relationship between rapid gain in weight and the retention of
either chloride or nitrogen.   He concluded that when chloride was
retained water also was retained and that there was a simultaneous
increase in body weight.   This relationship between chloride and
water balance was soon confirmed by other investigators (Nobécourt
and Vitry 1904, Widal and Javal 1904, Gruner 1906), but in 1910
Meyer showed that it was sodium and not the chloride radicle which
influenced the retention of water.

MICRO-ANALYTICAL CHEMISTRY

To acquire knowledge of chemical processes in childhood it was
essential to devise means whereby quantitative determinations could
be made on small samples of blood.   That suitable methods were
devised is a tribute to the industry of a few chemists and physicians
which in a generation transformed paediatrics.

The earliest " micro-methods" were introduced before 1910 and
were so designated because samples of less than 10 millilitres now
replaced samples of 100 millilitres (Mellman and Anke 1959).   The
term applies nowadays only to methods which require less than 1
millilitre of blood, plasma or serum.

The classical method for the estimation of serum calcium by the
weighing/

weighing of calcium oxide was not only laborious but demanded a large sample. Gravimetric methods had to be abandoned because the measurement by weighing of a light salt present in low concentration demanded either a large sample of serum or greater accuracy in weighing than was attainable with the laboratory equipment then in use. The introduction of volumetric methods provided simpler techniques applicable to smaller samples. By 1921 several methods had been described which depended on the precipitation of calcium oxalate and its titration with potassium permanganate. One of these (Kramer and Tisdall 1921) with slight modification has stood the test of time and can be applied to a sample of less than 1 millilitre.

One gravimetric method for the simultaneous determination of sodium and potassium had to be discarded because it required at least 5 millilitres of serum, but another, introduced later for the estimation of sodium alone, required only 1 millilitre of serum because it depended on the precipitation of sodium zinc uranyl acetate, a very heavy salt. Further reduction in the volume of samples became possible only with the development of titrimetric and colorimetric methods, and the precision of colorimetric methods was later increased by the use of the photo-electric colorimeter (Evelyn 1936). By the precipitation of sodium zinc uranyl acetate or sodium pyroantimonate the estimation of sodium could then be performed/

performed on 0.5 millitre of serum, and by the formation of potassium sodium cobaltinitrate the estimation of potassium on a sample of equal volume (Yoshimatsu 1927, King et al. 1942).

The invention of the flame photometer permitted the measurement of sodium and potassium in samples of 0.1 millilitre (Domingo and Klyne 1949). When the sample is introduced into a flame of propane, acetylene or coal gas, the intensity of the colour of the burning metal is dependent upon its concentration in the sample and is measured with a photo-electric colorimeter.

The term "ultra-micro method" has been introduced to describe techniques which require samples of less than 0.1 millilitre, and Natelson (1957) has expressed the opinion that it is now anachronistic to refer to any of the earlier methods as " micro-methods". When the accuracy of these new methods is established and they are adopted, capillary blood will suffice to supply adequate samples. This will be of particular advantage in paediatric practice especially when multiple or repeated estimations are needed.

DISORDERS OF CALCIUM, POTASSIUM AND SODIUM BALANCE IN CHILDHOOD

In 1912 before the advent of chemical micro-analysis in paediatrics an editorial in the Archives of Pediatrics echoed Claude Bernard by suggesting that close attention should be given to the possibility that disorders of the "absorption, retention and ultimate utilization" of salts might cause disease in childhood.

The/

The understanding of chemical metabolism in health and disease increased as methods of chemical analysis became simpler and more precise. Pre-eminent among the workers in this field was James Gamble whose many contributions culminated in a masterly synthesis of current knowledge in his "Chemical Anatomy, Physiology and Pathology of Extracellular Fluid" (1949). Here he drew attention to the precision with which the balance between cations and anions of the extracellular fluid is regulated, and to its resilience even under the most adverse conditions.

The advance in knowledge of disorders of calcium, potassium and sodium balance during the last fifty years has been so rapid that it defies chronological review. Attention will therefore be confined to the biochemistry of six important disorders of childhood, and the diseases selected are those with which my electrocardiographic studies are concerned.

Hypocalcaemic tetany

The cause of spasmophilia or infantile tetany perplexed and eluded the paediatrician during the early years of this century. It was known to be associated in some way with infantile rickets (Quest 1905), and in 1911 Neurath reported that the calcium content of the blood was low in spasmophilia. Not until 1918 however was conclusive evidence produced. Howland and Marriott then showed that in health the serum calcium was between 10 and 11 milligrams

per/

per 100 millilitres, that in rickets without tetany it might fall
to 8 milligrams, but that in infantile tetany it might be as low
as 3.5 milligrams.

This discovery not only provided a chemical explanation for
spasmophilia but heralded the recognition of tetany as a clinical
manifestation of a deficiency of ionized calcium, irrespective of
its cause.   It appeared to give a rational basis for the treatment
of tetany with calcium chloride, but it is apparent from the work
of Gamble, Ross and Tisdall (1923) and of Anderson and Graham
(1924-25) that the favourable effect of this treatment resulted as
much from the metabolic acidosis which it produced (thereby
increasing the ionization of calcium) as from an increase in the
total calcium of the serum.

In recent years infantile rickets has virtually disappeared
and with it the principal cause of hypocalcaemia in childhood.
Hypocalcaemia may however still be encountered in some special
types of rickets such as those associated with resistance to vitamin
D (R.R.D.), with the de Toni-Fanconi syndrome or with coeliac disease.

A few cases of hypocalcaemia occur in association with tetany
during the first week or so of life.   In these cases of neonatal
tetany, hyperphosphataemia is invariably present and may be the
factor which predisposes to hypocalcaemia.   It has been pointed
out that the kidney of the newly-born cannot readily achieve
adequate/

adequate clearance of phosphate and that affected infants have fed
on cow's milk which contains more phosphorus than does human milk
(Gardner et al. 1950, Gittleman and Pincus 1951).

Depletion of ionized calcium may also be induced in newborn
infants during replacement transfusion with citrated blood. This
reduction in the ionized but not in the total serum calcium is
attributed to the formation of calcium citrate which is a poorly
ionized salt (Cantarow 1959).

Infantile diarrhoea

Infantile diarrhoea, infantile gastro-enteritis and the
"cholera infantum" of earlier writers are regarded as synonymous.
The last description emphasizes the possible severity of the
dehydration and of the metabolic disturbance, and implies that in
asiatic cholera alone can they find a parallel.

The outstanding chemical disturbance is a metabolic acidosis
arising from the loss of large amounts of sodium, potassium and
bicarbonate in the stools (Holt, Courtney and Fales 1915). The
loss of sodium in the faeces causes depletion of extracellular
sodium. This is said to lead to the migration of potassium from
the intracellular to the extracellular fluid in order to restore
osmotic balance, and thus to an intracellular deficit of potassium
(Darrow 1946). Glycogenolysis occurs if the intake of carbohydrate
is inadequate, and this process also releases potassium from the
intracellular/

intracellular fluid.   Provided that renal function is unimpaired there is a continuous loss into the urine of extracellular potassium (Holliday and Egan 1959).   At first the extracellular concentration of potassium is maintained at the expense of the intracellular potassium.   As the loss of potassium continues from the kidney, and especially if it is also lost through vomiting, the amount of potassium in the extracellular fluid also falls.

A more profound disorder may be provoked by the excessive administration of hypotonic fluid.   If by this means the extra-cellular fluid is rendered hypotonic still more potassium will pass from the cells to restore osmotic balance.

It would be incorrect to suggest that manifest depletion of potassium is always or even frequently encountered nowadays during the course of infantile gastro-enteritis but it is evident that it is more likely to occur when diarrhoea and vomiting are severe.

Another syndrome which may occur during the treatment of infantile diarrhoea has recently aroused interest.   This disorder has been named hypernatraemic dehydration, hypertonic dehydration or, simply, hypernatraemia, and its features have been described by Rapoport (1947), Weil and Wallace (1956) and by Finberg and Harrison (1955, 1959).   There is excessive retention of sodium in the extra-cellular fluid.   The predisposing factor is thought to be an excessive loss of water not only in the faeces because of diarrhoea, but also from the lungs because of acidotic breathing.   The

disorder/

disorder is precipitated by the administration of large quantities of sodium, and a contributory factor in early infancy may be the immaturity of renal function which tends to prevent the excretion of a highly concentrated urine (Young and McCance 1942). Sclerema and pitting oedema are constant, but the clinical features may also include hypertonicity of muscles, head retraction, convulsions and impairment of consciousness. Even if the infant survives, the neurological disorder may persist. The converse of this sequence of events has been observed in patients who have developed hypernatraemia while suffering from an intracranial lesion such as hydrocephalus or subdural haematoma (Cooper and Crevier 1952).

Diabetic coma

The rapid development of severe ketonaemia is recognised as a characteristic feature of diabetes in childhood (White 1933, Gamble 1949). The metabolic acidosis resulting from the accumulation of ketone bodies, the catabolism of tissue associated with gluconeogenesis, and the loss of water resulting from polyuria, vomiting and hyperventilation, combine to produce a severe disorder of potassium metabolism.

In untreated diabetic coma the serum potassium may be within normal limits or even raised, and does not reflect the overall depletion of potassium from the body. This is partly due to the migration of potassium from cells to extracellular fluid to replace sodium lost in the urine with the excessive quantities of keto-acids/

acids to be excreted, and partly to the release of potassium from cells as a result of gluconeogenesis. Extracellular potassium is lost continuously from the kidney (Atchley et al. 1933) and the total deficit of potassium is further increased by its loss in vomitus.

When treatment is instituted there may be a precipitous fall in the concentration of potassium in the extracellular fluid. The administration of insulin and glucose permits glycogenesis and this process leads to the transfer of potassium from extracellular fluid. The administration of water increases the volume of the extra-cellular fluid and so decreases its concentration of potassium. The administration of sodium leads to the return of potassium from the extracellular fluid to the cells. Treatment therefore adds extracellular depletion of potassium to the existing overall deficit in the body, and it is at this stage that the clinical features of potassium deficiency may appear.

Renal failure

Both chronic renal failure and acute renal failure are encountered in childhood. Chronic failure may mark the terminal stage of such disorders as renal hypoplasia, chronic pyelonephritis, nephrosis, anaphylactoid purpura and the de Toni-Fanconi syndrome. Acute failure may be the result of intravascular haemolysis, sulphonamide/

sulphonamide crystallization in the renal tubules or thrombosis of renal veins.

Metabolic acidosis is produced by failure to excrete the acid waste products of metabolism, and by the loss of sodium because of failure of the kidney to elaborate ammonia. The renal clearance of potassium is diminished because of impaired glomerular filtration, and this leads to hyperkalaemia. Retention of phosphate leads to hyperphosphataemia and thus to increased parathyroid activity. This secondary hyperparathyroidism causes hypercalciuria and this in turn causes hypocalcaemia.

Adrenocortical failure

Sudden failure of the adrenal cortex in childhood may occur in the course of fulminating infections especially meningococcaemia, in the congenital or foetal adrenogenital syndrome and in Addison's disease (Jaudon 1946, Iversen 1955, Bongiovanni 1959). Hyponatraemia results, and the severity of the hypotonic dehydration may be so great as to cause profound shock or even sudden death.

This catastrophe is associated with adrenal haemorrhage in meningococcal septicaemia, with failure of the cortex to elaborate cortisol in the congenital adrenogenital syndrome (Jailer et al. 1956), and with adrenal tuberculosis or hypoplasia in Addison's disease. In each instance a reduction of aldosterone-like activity profoundly affects renal tubular absorption, and allows the excretion/

excretion of large amounts of sodium, chloride and water, but
promotes the excessive retention of potassium. Although the
chemical disorder in the adrenogenital syndrome suggests hypo-
aldosteronism the abundant excretion of aldosterone in the urine
indicates that production of the hormone is not at fault (Grumbach
and Luetscher 1956).

Severe hyperkalaemia may occur but tends to be overshadowed
by the depletion of sodium and water which may be so great as to
precipitate circulatory failure. This catastrophe apart, reduction
of blood volume leads to diminished glomerular filtration, to the
retention of the waste products of metabolism and so to a metabolic
acidosis. Impairment of glucocorticoid activity leads to hypo-
glycaemia and glycogenolysis, and so to an increase in extracellular
potassium.

Treatment of adrenocortical failure by means of substances
such as hydrocortisone, fludrocortisone and deoxycortone (D.C.A.)
tends to produce hypokalaemia by increasing the urinary output of
potassium. When glycogenesis is stimulated the extracellular
content of potassium is further reduced.

Idiopathic hypercalcaemia

Until a few years ago hypercalcaemia was seldom encountered
in paediatric practice. Such causes as hyperparathyroidism,
sarcoidosis, immobilization osteoporosis and the milk and alkali
syndrome/

syndrome, rare at any age, are extremely so in children.   Hyper-
calcaemia has recently been detected in infants suffering from
interstitial plasma cell pneumonia, but this cause is also rare
(Hallman, Tähkä and Ahvenainen 1954).

In 1952 (a,b) Lightwood drew attention to a clinical syndrome
which resembled hyperchloraemic renal acidosis (Lightwood 1935).
Payne (1952) described the chemical features of this new disease.
Hypercalcaemia is the outstanding chemical abnormality but there is
neither the hyperchloraemia nor the excessive renal loss of
bicarbonate which characterize renal acidosis.   The clinical
features of the disease, to which the name "idiopathic hypercalcaemia"
has been given, are anorexia, failure to thrive, obstinate constipa-
tion, mild dehydration and thirst.   The age at onset is between 3
weeks and 11 months (Graham 1959).   The disease is usually of short
duration and benign but those few patients who have died have had
extensive renal medullary calcinosis (Dawson and Craig 1954, Rhaney
and Mitchell 1956).

In addition to this benign or mild type of idiopathic hyper-
calcaemia there is a severe or malignant form which shows the same
clinical features together with mental retardation, microcephaly,
hypertension, cardiac murmurs, osteosclerosis and nitrogen retention
(Butler 1951, Fanconi and Girardet 1952, Schlesinger et al. 1952).
This severe form is rare.   Its relationship to the milder disorder
is still open to doubt (Lightwood and Stapleton 1953), but the
reported/

reported occurrence of cases of intermediate severity (Joseph and Parrott 1958) suggests that the two syndromes are merely variants of a single disease.

The precise aetiology of these disorders is unknown but that they are in some way associated with the intake of vitamin D is at present the most acceptable hypothesis (Lowe et al. 1954, Carter et al. 1955). It is quite clear however that they are not the expression of poisoning with enormous doses of vitamin D, and indeed the amount of vitamin D ingested by patients has often not exceeded the average prophylactic dose given to healthy infants (Creery and Neill 1955). Forfar and his colleagues (1956) have objected to the postulated association of vitamin D intake and idiopathic hyper-calcaemia on the grounds that hypercholesterolaemia and hypocitraemia are features of this disease, but not of vitamin D poisoning. Rapid improvement in the clinical and biochemical status of patients does however occur when the intake of vitamin D ceases and that of calcium is reduced.

It has recently been shown that patients with severe idiopathic hypercalcaemia have an extremely high concentration of vitamin D in the plasma which may persist many months after the intake of vitamin D has ceased (Fellers and Schwartz 1958, Smith et al. 1959). The hypothesis which seems to fit most of the available evidence is that the disease is a response to the administration of vitamin D to infants with a primary defect in the metabolism of vitamin D (Bongiovanni et al. 1957, B.M.J., 1960).

CALCIUM, POTASSIUM AND SODIUM IN MYOCARDIAL ACTIVITY

The detection of disorders of calcium, potassium and sodium balance has been made possible by the development of suitable biochemical techniques, but it is still important for the paediatrician to evaluate any other technique by which he might obtain the same information without recourse to venipuncture. It is therefore now opportune to consider the influence of these metals on the action of the heart, and the action of the heart as interpreted by the electrocardiogram as an indicator of their concentration in the body fluids.

To Sidney Ringer (1883) belongs the distinction of having demonstrated the dependence of myocardial activity on the presence of salts of calcium, potassium and sodium. He observed that when perfused with a solution of sodium chloride the frog heart soon ceased to beat, and that it was necessary to add both calcium and potassium to the perfusing fluid for contraction to continue. He concluded that contraction of the heart was regulated by the antagonising action of calcium and potassium salts. This concept of the chemistry of myocardial activity was soon confirmed, and it was accepted as being equally applicable to the human heart (Beaunis 1888, Howell 1906).

It has been confirmed that the toxic effect of potassium on the myocardium is to increase the length of diastole until eventually the heart stops in diastole, a condition known as potassium

inhibition/

inhibition, whereas with calcium intoxication systole lengthens and cardiac standstill takes place in systole, a condition known as calcium rigor (Best and Taylor 1945). The contribution made by sodium to myocardial function awaits greater definition but the presence of this metal has long been considered necessary for the contraction of muscle (Overton 1902).

In the light of the profound influence of potassium and calcium upon the myocardium it was to be expected that electro-cardiographic signs would be found in patients suffering from disorders of potassium or calcium metabolism. This has been confirmed and descriptions have been given of the changes found in association with hypercalcaemia, hypocalcaemia, hyperkalaemia and hypokalaemia. It is agreed that all of these disorders may affect the length of intervals in the electrocardiogram and that changes in the concentration of potassium may alter the contour of waves.

The electrocardiograph would appear to provide the clinician with a convenient reflection of the composition of the tissue fluid perfusing the cardiac musculature in terms of its content of potassium and calcium. For this reason the electrocardiogram has been considered to be of value in the diagnosis of disorders of potassium and calcium balance and as a guide to the control of subsequent therapy (Merrill et al. 1950, Keith, Rowe and Vlad 1958, Brusilow and Cooke 1959). It is clear however that the electro-cardiogram/

cardiogram cannot afford more than a reflection because many factors can influence the record and several of these may act together.

The electrocardiogram in chronic renal failure furnishes an excellent example of multiple influences, for in this disorder hyperkalaemia may be found together with hypocalcaemia, while the concomitant acidosis can produce electrocardiographic changes similar to those of hyperkalaemia even in the presence of potassium depletion (Levine 1954). Moreover the electrocardiographic signs of hyperkalaemia are said to appear when the serum potassium is only slightly raised if there is coexisting depletion of calcium or of sodium (Merrill et al. 1950).

There is another possible source of error. Primary defects of the conducting system and of the myocardium may profoundly affect the electrocardiogram and if these coexist with a disorder of calcium or potassium balance one might reasonably expect the electrocardiographic response to the latter to be altered or over-shadowed.

Electrocardiography is therefore an indirect method for the assessment of disorders of calcium and potassium balance and as with many other tests used in clinical medicine caution has to be exercised in the interpretation of results. Nevertheless the place of electrocardiography in the investigation of disorders of calcium and potassium metabolism in early childhood requires special consideration/

consideration for suitable samples of venous blood may be difficult to obtain and repeated venipuncture is undesirable.

THE ELECTROCARDIOGRAM

INTRODUCTION

Electrocardiography in Idiopathic Hypercalcaemia and other

Cation Disorders of Childhood

T H E   A U T H O R 'S   I N V E S T I G A T I O N S

I N T R O D U C T I O N

PART I   Time intervals in the electrocardiogram of healthy infants.

PART II   Electrocardiography in idiopathic hypercalcaemia of infancy.

PART III   Vitamin D and heart lesions in the rabbit.

PART IV   Electrocardiography in hypocalcaemia, hyperkalaemia, hypokalaemia and hypernatraemia.

INTRODUCTION

The prevalence of hypercalcaemia in early childhood provided the stimulus for these investigations. During the treatment of idiopathic hypercalcaemia close attention must be paid to the concentration of serum calcium, and this necessitates frequent venipuncture. In an attempt to provide an alternative to biochemical analysis it was decided to assess the accuracy of the electrocardiographic response to hypercalcaemia in this disease.

Electrocardiograms were recorded from 25 patients suffering from idiopathic hypercalcaemia. To resolve unexpected difficulties in interpretation, their electrocardiograms were compared with those of healthy infants. For this purpose the electrocardiograms of one hundred healthy infants were recorded with the same technique, and measurements were made of the various waves and intervals. This control material is studied in Part I, and the electrocardiography of idiopathic hypercalcaemia in Part II.

It then seemed that certain features of the electrocardiogram in idiopathic hypercalcaemia might be accounted for by lesions of the heart caused by vitamin D. An attempt was made to explore this possibility by a post-mortem study of rabbits which had received large doses of vitamin D. This is described in Part III.

The difficulties which had been encountered in the interpretation of the electrocardiogram in idiopathic hypercalcaemia prompted

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a study of electrocardiographic patterns in hypocalcaemia, hyper-
kalaemia, hypokalaemia and hypernatraemia. Twelve patients were
examined and this study is described in Part IV.

Electrocardiographic examinations were virtually confined to
the standard limb leads because it was concluded from the work of
other investigators that these should suffice for the detection of
changes due to disturbances of calcium or potassium balance. More-
over, in very young children these leads are the most easily recorded
and therefore the most likely to furnish records suitable for
analysis. This consideration was particularly important because a
photographic electrocardiograph was used and hypnotic drugs were not
given.

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Author's Investigations

PART I

<u>TIME INTERVALS IN THE ELECTROCARDIOGRAM</u>

<u>OF HEALTHY INFANTS</u>

ELECTROCARDIOGRAPHY IN IDIOPATHIC HYPERCALCAEMIA AND OTHER CATION DISORDERS OF CHILDHOOD

PART I

TIME INTERVALS IN THE ELECTROCARDIOGRAM OF HEALTHY INFANTS

PREAMBLE

Fifty years have passed since Funaro and Nicolai (1908) gave the first description of the electrocardiogram in childhood based on a study of the first standard limb lead of 45 healthy children. In 1913 Hecht published an account of the duration of various events in the cardiac cycle of healthy children and described the features of sinus arrhythmia.

It is now accepted that there are substantial differences between the electrocardiograms of children and of adults (Mannheimer 1940/

1940, Tudbury and Atkinson 1950).

Several studies have been made of the electrocardiogram of healthy children. Some observers have described the variations in the electrocardiogram throughout childhood (Hafkesbring et al. 1937, Burnett and Taylor 1936, Ziegler 1951); some have paid little or no attention to infancy (Perry 1931, Grenet et al. 1939, Switzer and Besoain 1950) while others have dealt exclusively with that period (Engel 1937-8, Nádrai 1938-9, Groedel and Miller 1944). These descriptions make it clear that the greatest amount of variation in the electrocardiogram of the healthy child takes place during the first year of life and for this reason normal or average values must be known so that the abnormal may be recognized.

Appreciable disagreement exists between various series of figures relating to the duration of intervals in the electrocardiogram of infants and the present investigation was conducted against this background.

MATERIAL AND METHODS

One hundred subjects were examined, twenty-five in each quarter of the first year of life. Their ages ranged from 2 to 51 weeks, and the mean was 24.5 weeks. Fifty-eight were boys and forty-two, girls. They were examined while visiting the Child Welfare Clinic at the Royal Hospital for Sick Children, Glasgow. None showed clinical/

clinical evidence of heart disease and in none was there any reason to suspect a disorder of mineral metabolism. From ten subjects two electrocardiograms were obtained at an interval of 10 to 17 weeks. Measurements used for analysis were derived from the second electro-cardiogram but certain comparisons were made between the two records.

No sedative was given. The standard limb leads were recorded simultaneously with the infant in the recumbent position. The average heart rate was calculated from the average length of cardiac cycles, and any arrhythmia noted. Measurements were made of the length of the P wave, PR (PQ) interval, QRS complex, T wave, ST segment and QT interval (Fig. 1). The QT interval was corrected to compensate for the influence of heart rate by means of Bazett's formula (1920) and the resulting value is referred to as QTc. The technique adopted for the recording and reading of electrocardio-grams is described in Appendix I.

The arithmetic mean and the standard deviation (S.D.) of the heart rate and of each interval and wave was calculated for each quarter and for the entire sample. Coefficients of correlation (r) were calculated to relate the length of the P wave, PR interval, QRS complex, T wave, QT interval and ST segment to the heart rate and to age. Complete positive correlation would be indicated by a value for r of +1, complete absence of correlation by a value of 0 and complete negative correlation by a value of -1. The correlation coefficients/
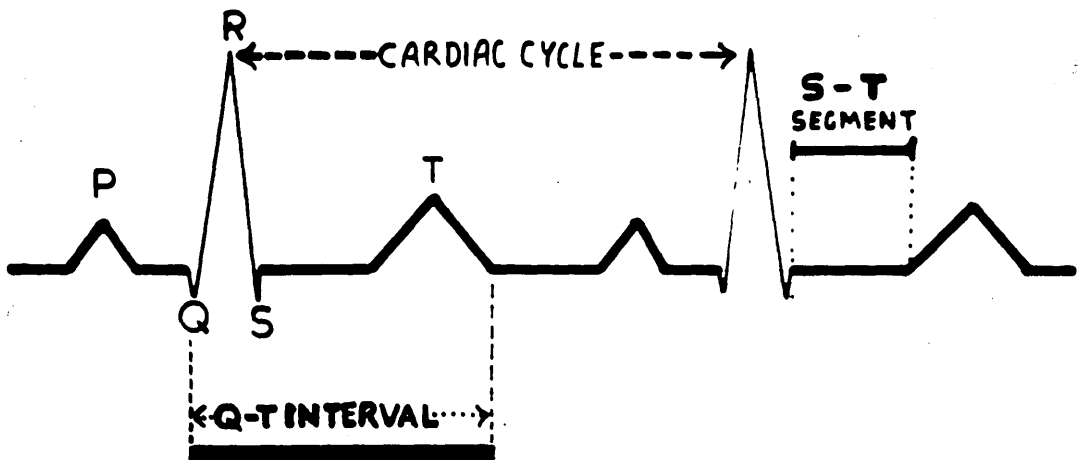
Fig. 1. Diagram showing the nomenclature used in describing the cardiac cycle in healthy infants.

coefficients were tested for significance and linear regression equations were formulated to express the relationship between these intervals and heart rate and age.   The data on which these calculations were based, the frequency distribution tables and the details of the statistical analysis are contained in Appendices II to IV.

RESULTS AND DISCUSSION

Heart rate

The lowest rate encountered was 102 per minute at the age of 40 weeks, and the highest 207 per minute at the age of 2 weeks. The average rate for the entire sample was 141 per minute, but the average rate in the fourth quarter was 20 beats per minute less than that in the first (Table I).   An unexpected finding was that

TABLE I

Heart Rate (per minute) and Arithmetic Mean of Cardiac Cycle (seconds)

Age Group	No. of Observations	Range of Observations	Arithmetic Mean of Rate	S.D.	Arithmetic Mean of Cycle
2 wks. – 3 mths.	25	118 – 207	155.6	22.32	0.39
3 mths. – 6 mths.	25	118 – 200	143.2	21.47	0.42
6 mths. – 9 mths.	25	115 – 182	130.5	13.52	0.46
9 mths. – 12 mths.	25	102 – 200	135.6	22.88	0.44
2 wks. – 12 mths.	100	102 – 207	141.2	22.31	0.42

the/

the mean rate in the third quarter was less than that in the fourth.
In 47 of the 100 observations the heart rate was between 120 and 139
per minute, and in 80 it lay between 100 and 159 per minute. Eleven
of the 20 subjects whose heart rate exceeded 159 per minute were less
than 3 months old, and 6 were between 3 and 6 months old. A highly
significant negative correlation of heart rate with age was disclosed
($r = -0.2921$, $p < 0.01$).

It is obvious that these heart rates cannot be regarded as basal
or resting values because some subjects were excited by the distur-
bance inherent in the recording procedure. Nevertheless, as Ziegler
(1951) has pointed out such measurements give a useful indication of
the wide range through which the heart rate may vary in health. No
one would deny that the heart rate should be counted during sleep
(Nadas 1957), but in infancy this is not always practicable.

Published figures for the heart rates of normal infants show
wide variations but a feature common to most is that the rate
declines as age increases. A satisfactory measure of agreement
exists between the values obtained in this series and those reported
by Seham (1921, 1924), Nádrai (1938-39) and Ziegler (1951).

Arrhythmia

Sinus arrhythmia was the only disturbance of cardiac rhythm
encountered. The diagnosis, based on the criterion proposed by
Krumbhaar and Jenks (1916), was made only if the greatest difference
between/

between cardiac cycles was 0.1 second or more.   Five examples were found.   The subjects were 4, 7, 9, 10 and 11 months old, and had average heart rates of 128, 120, 102, 110 and 133 per minute, respectively.   The infrequency of sinus arrhythmia in this sample lends support to the opinion of several authors, including Lincoln and Nicolson (1928), that this arrhythmia is less common in infancy than in later childhood and that its incidence rises as the heart rate falls.

The infant with sinus arrhythmia at the age of 10 months had been examined 11 weeks before.   In the earlier record the difference of 0.04 second between cardiac cycles was insufficient to warrant a diagnosis of sinus arrhythmia.   There was little difference between the average heart rates of the two records, (115 in the first, 110 in the second), and this suggests that slowing of the pacemaker is not the sole factor causing sinus arrhythmia.

Differences in the length of cardiac cycles of less than 0.1 second were found in 69 electrocardiograms, but unlike true sinus arrhythmia the incidence was not substantially greater in older infants.   There were 17 examples in the first quarter, 16 in the second, 19 in the third and 17 in the fourth.

P wave

The duration of the P wave was from 0.04 to 0.08 second, and the mean values increased with age (Table II).   There was a highly

TABLE II/

TABLE II

P wave (seconds)

Age Group	No. of Observa- tions	Range of Observa- tions	Arith- metic Mean	S.D.
2 wks. – 3 mths.	25	0.04–0.07	0.058	0.0060
3 mths. – 6 mths.	25	0.06–0.08	0.066	0.0071
6 mths. – 9 mths.	25	0.06–0.08	0.066	0.0057
9 mths. – 12 mths.	25	0.06–0.08	0.069	0.0122
2 wks. – 12 mths.	100	0.04–0.08	0.065	0.0081

significant positive correlation (p < 0.01) between the length of the wave and age (r = +0.5045). This lengthening of the P wave with increasing age accords with Ziegler's findings (1951), but his mean values are as much as 0.012 second less. There was no significant correlation between the length of the P wave and the heart rate (r = -0.1003). It is probable that the increasing width of the P wave observed during the first year of life reflects the increasing mass of the atria.

PR interval

The mean duration of the PR interval in the sample was 0.104 second and individual values lay between 0.08 and 0.14 second (Table III). The mean PR interval increased from the first to the

TABLE III/

<u>TABLE III</u>

PR interval (seconds)

Age Group	No. of Observations	Range of Observations	Arithmetic Mean	S.D.
2 wks. – 3 mths.	25	0.08–0.14	0.099	0.0127
3 mths. – 6 mths.	25	0.08–0.13	0.102	0.0111
6 mths. – 9 mths.	25	0.09–0.14	0.111	0.0138
9 mths. – 12 mths.	25	0.08–0.13	0.105	0.0172
2 wks. – 12 mths.	100	0.08–0.14	0.104	0.0134

third quarter, but was less in the fourth quarter than in the third. This suggested that the PR interval might be more closely related to heart rate than to age because, as already noted, the mean heart rate was greater in the fourth quarter than in the third.

There was a significant correlation ($p < 0.05$) between the length of the interval and both heart rate ($r = -0.2302$) and age ($r = +0.2034$), but the influence of heart rate was the more important. Thus the PR interval tends to lengthen both with decreasing heart rate and with increasing age. Alimurung and Massell (1956) came to the same conclusion, but Schlamowitz (1946b) and Savilahti (1946b) doubted whether its length was influenced by the heart rate.

The mean values obtained for the length of the PR interval are lower than those given by Burnett and Taylor (1936) and by Epstein (1948).

<u>QRS complex and T wave</u>/

QRS complex and T wave

The duration of the QRS complex lay between 0.05 and 0.08 second, and the mean value for the entire sample was 0.062 second (Table IV).   The quarterly means increased progressively with age.

TABLE IV

QRS complex (seconds)

Age Group	No. of Observations	Range of Observations	Arithmetic Mean	S.D.
2 wks. – 3 mths.	25	0.05-0.07	0.057	0.0069
3 mths.– 6 mths.	25	0.05-0.07	0.059	0.0057
6 mths.– 9 mths.	25	0.05-0.07	0.064	0.0064
9 mths.– 12 mths.	25	0.06-0.08	0.067	0.0062
2 wks. – 12 mths.	100	0.05-0.08	0.062	0.0074

Very significant correlations ($p = < 0.01$) existed between the length of the QRS complex and both age ($r = +0.5287$) and heart rate ($r = -0.4351$), but the influence of age was the more important. The QRS complex therefore lengthens with increasing age or decreasing heart rate, and this is in agreement with the opinion expressed by Savilahti (1946a).   The mean values given by Ziegler (1951) are greater, but the mean values given by Seham (1924) and by Burnett and Taylor (1936) are lower than those found in this study.   Indeed Seham's mean value is so low that it seems possible that he may have ignored/

ignored shallow Q waves when making his measurements.   Close

agreement does however exist between the present figures and those of

Jundell and Stenström (1931).

The length of the T wave lay between 0.09 and 0.15 second, and

the mean value for the entire sample was 0.120 second (Table V).   A

TABLE V

T wave (seconds)

Age Group	No. of Observations	Range of Observations	Arith- metic Mean	S.D.
2 wks. – 3 mths.	25	0.09-0.14	0.111	0.0136
3 mths. – 6 mths.	25	0.10-0.15	0.115	0.0129
6 mths. – 9 mths.	25	0.11-0.15	0.126	0.0112
9 mths. – 12 mths.	25	0.11-0.15	0.129	0.0139
2 wks. – 12 mths.	100	0.09-0.15	0.120	0.0146

gradual increase in the mean length of the T wave occurred from the

first to the fourth quarter, and this trend is in agreement with

the findings of Ziegler (1951) but his values are greater.   A highly

significant degree of correlation ($p = <0.01$) was discovered between

the duration of the T wave and both age ($r = +0.3288$) and heart rate

($r = -0.7124$) but the influence of rate was by far the more important.

Both the QRS complex and the T wave lengthen throughout the first

year of life, and it seems likely that this reflects the growth of the

ventricles/

ventricles.

QT interval

The QT interval includes the QRS complex, the ST segment and the T wave.

The range through which the QT interval varied during infancy was found to be 0.21 to 0.29 second, with a mean value of 0.257 second (Table VI).   These means are greater than those reported by

TABLE VI

QT interval (seconds)

Age Group	No. of Observa- tions	Range of Observa- tions	Arith- metic Mean	S.D.
2 wks. – 3 mths.	25	0.21–0.28	0.250	0.0186
3 mths. – 6 mths.	25	0.21–0.28	0.252	0.0141
6 mths. – 9 mths.	25	0.22–0.29	0.264	0.0150
9 mths. – 12 mths.	25	0.23–0.29	0.264	0.0175
2 wks. – 12 mths.	100	0.21–0.29	0.257	0.0174

Ziegler, but the mean for the whole year is less than that given by Kirchoff and del Campo (1954).

Bazett (1920) recognised that the length of the QT interval was affected by the heart rate, and in the belief that the relationship could be expressed by a straight-line graph, he introduced a formula to express such an association.   Some investigators have suggested that/

that the relationship is not linear, and have devised other methods

for relating the measured QT interval to the heart rate (Fridericia

1920, White and Mudd 1929, Ashman and Hull 1945, Schlamowitz 1946a).

The individual measurements of the QT interval were plotted

against the heart rate and it was obvious that the QT interval

lengthened as the heart rate fell (Fig. 2).   This is shown statisti-

cally by a very significant negative linear correlation ($r = -0.8572$,

$p = <0.01$).   A very significant positive correlation existed between

the QT interval and age ($r = +0.3275$, $p = <0.01$), but the influence

of age was much less than that of rate as is shown by the linear

regression of QT on age and heart rate (Appendix IV).

The range of QTc values for the whole period under review was

0.36 to 0.42, with a mean of 0.393 (Table VII).   A survey of the

TABLE VII

QTc

Age Group	No. of Observations	Range of Observations	Arith- metic Mean	S.D.
2 wks. – 3 mths.	25	0.37–0.415	0.399	0.0116
3 mths. – 6 mths.	25	0.365–0.41	0.388	0.0110
6 mths. – 9 mths.	25	0.36–0.415	0.390	0.0153
9 mths. – 12 mths.	25	0.375–0.42	0.393	0.0134
2 wks. – 12 mths.	100	0.36–0.42	0.393	0.0133

findings/

Fig. 2. Healthy infants: Scatter diagram of 100 values for QT related to the heart rate. The coefficient of correlation ($r = -0.8572$) is very significant ($p = <0.01$).

findings of other investigators discloses appreciable differences between their mean values. Epstein (1948) and Lyon and Kaplan (1954) accepted a value of 0.38. Alimurung and his colleagues (1950) and Yu, Joos and Katsampes (1951) accepted a value of 0.404. Ziegler (1951) found the mean values between the ages of one week and one year to lie between 0.385 and 0.408, and the scatter of individual observations seems to have been very much wider than in the present sample in which 97% of all values fell within the range, mean $\pm$ 2 x S.D., and 76% within the range, mean $\pm$ 1 x S.D.

ST segment

The length of the ST segment was examined because this portion of the QT interval appears to be particularly susceptible to changes in the concentration of calcium in the body fluids. It seemed possible that measurement of the ST segment might permit the recognition of significant changes in its length too small to lengthen or shorten the QT interval to an appreciable extent.

The length of the ST segment lay between 0.05 and 0.11 second with a mean value of 0.075. It was observed from the mean values for the four quarters that this interval shortened with increasing age (Table VIII). Highly significant negative correlations ($p = <0.01$) existed between the length of the segment and both age ($r = -0.3554$) and heart rate ($r = -0.2583$). In other words, the

TABLE VIII/

TABLE VIII

ST (seconds)

Age Group	No. of Observations	Range of Observations	Arithmetic Mean	S.D.
2 wks. – 3 mths.	25	0.06–0.11	0.081	0.0153
3 mths. – 6 mths.	25	0.06–0.10	0.078	0.0116
6 mths. – 9 mths.	25	0.05–0.10	0.075	0.0126
9 mths. – 12 mths.	25	0.05–0.08	0.068	0.0082
2 wks. – 12 mths.	100	0.05–0.11	0.075	0.0127

ST segment tended to shorten not only with increasing age but also with increasing heart rate.

Thus in this sample the QRS complex and the T wave lengthened with increasing age but the ST segment shortened. This association with age received corroboration from a comparison of the components of the QT interval of the 10 subjects twice examined. In the second electrocardiogram the QRS complex had lengthened or remained unchanged in 10 subjects, the T wave in 7, but the ST segment had shortened or remained unchanged in 8.

CONCLUSIONS/

CONCLUSIONS

The standard limb leads of the electrocardiograms of 100 healthy infants were examined.

The heart rate shows wide fluctuations throughout infancy but tends to decrease as age increases.

Sinus arrhythmia occurs seldom in infancy. Only five examples were encountered, three of which were in the age group, 9 - 12 months. Smaller differences in the length of cardiac cycles occur frequently throughout infancy. No other type of arrhythmia was observed.

The P wave, PR interval, QRS complex and T wave lengthen with increasing age, and, the P wave excepted, with slowing of the heart. The ST segment shortens both with increasing age and increasing heart rate.

The profound influence of heart rate upon the length of the QT interval is confirmed; the interval lengthens as the heart rate falls. To permit comparisons between QT intervals recorded at different heart rates it is necessary to compensate for the influence of rate by the application to the measured QT interval of a correcting factor. The values for this corrected QT interval or QTc were from 0.36 to 0.42 in this series.

Author's Investigations

PART II

ELECTROCARDIOGRAPHY IN IDIOPATHIC HYPERCALCAEMIA

OF INFANCY

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ELECTROCARDIOGRAPHY IN IDIOPATHIC
HYPERCALCAEMIA AND OTHER CATION
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PART II

ELECTROCARDIOGRAPHY IN IDIOPATHIC
HYPERCALCAEMIA OF INFANCY

PREAMBLE

Before embarking upon an examination of the electrocardio-
graphic features of idiopathic hypercalcaemia of infancy I shall
devote some attention to the electrocardiographic changes
previously reported as being induced by hypercalcaemia. Electro-
cardiograms in idiopathic hypercalcaemia will be considered
against this background and their features compared with those
occurring in hypercalcaemia induced with calcium gluconate and
with those of electrocardiograms of healthy infants.

The/

The methods used for the recording and analysis of electrocardiograms were the same as those used during the examination of healthy infants and are described in Appendix I. Measurements of the duration of events in the cardiac cycle of patients from 2 weeks to 12 months of age were compared with those made in the electrocardiograms of healthy infants as described in Part I of the present investigations.

REVIEW OF LITERATURE

A survey of the literature reveals that two lines of approach have been made to the study of the effect of hypercalcaemia on the electrocardiogram. Some observers have confined their attention to electrocardiographic disturbances taking place during the administration of calcium salts, while others have described the electrocardiographic features of primary hyperparathyroidism and other diseases of which hypercalcaemia is a feature.

Hypercalcaemia induced by calcium salts

Singer (1921) gave calcium chloride intravenously in the treatment of heart failure, and Petzetakis (1924) reported that this salt could eliminate extrasystoles and interrupt paroxysmal tachycardia. Segall and White (1925) were unable to find any constant electrocardiographic abnormality following the administration of calcium chloride by mouth to human subjects.

Fujimori (1933) reported that bradycardia and shortening of the QT interval followed the intravenous injection of calcium chloride/

chloride, and that less frequently there was lengthening of the PR interval and depression of the P, R and T waves.   Berliner (1936) did not mention the QT interval, but found a depressed or inverted T wave in 92%, a depressed or inverted P wave in 54% and marked bradycardia in 67% of healthy subjects given calcium chloride intravenously.

Clarke (1941) studied the electrocardiograms of four patients with mitral valve disease who were given calcium chloride intravenously.   He concluded that the changes occurring during the injection were dependent upon the concentration of calcium in the blood.   The earliest changes were bradycardia, sinus arrhythmia, shifting of the pacemaker and various degrees of heart block.   The later and more severe changes included the appearance of idioventricular rhythm and of ventricular extrasystoles of "large and unusual form".

Furman, Hallerstein and Startzman (1951) described the electrocardiographic changes which followed the intravenous injection of calcium gluconate in infants undergoing replacement blood transfusion.   For a few minutes after the injection bradycardia, sinus arrhythmia and premature beats were observed.   In addition, but persisting for as long as fifteen minutes, the PR interval lengthened, the QT interval shortened and the T wave inverted.

Hypercalcaemia in clinical medicine

Hypercalcaemia/

Hypercalcaemia in clinical medicine

Hypercalcaemia is a feature of primary hyperparathyroidism and there is wide agreement that in this disease the QT interval is shortened (Ballin 1932, Kellogg and Kerr 1936, Korth and Hecht 1938, Bradlow and Segel 1956). Supporting the belief that the shortened QT interval is directly associated with the hypercalcaemia is the observation that the QT interval lengthens when the serum calcium falls after the removal of a parathyroid adenoma. Depression of the T wave has also been reported in this disease (Kellogg and Kerr 1936).

Shortening of the QT interval due to a short ST segment was regarded by Yu (1952) as characteristic of hypercalcaemia. Contrary to the usual experience, lengthening of the QT interval accompanied hypercalcaemia in two cases of myelomatosis reported by Levine (1954). The reason for this is not clear. Lengthening of the QT interval may signify a depletion of ionized calcium (Yu 1952). If, as Gutman and Gutman (1937) have shown, there is increased binding of calcium by protein in multiple myelomatosis, even in the absence of hyperproteinaemia, it is just conceivable that these patients may have been suffering from a deficiency of ionized calcium.

Shortening of the QT interval emerges from clinical and experimental evidence as an important sign of hypercalcaemia. Signs such/

such as heart block and premature systoles induced by the injection
of calcium may possibly result from hypercalcaemia of a degree seldom
encountered in clinical practice.   On the other hand sinus arrhythmia
is too common in childhood for it to be of value as a sign of hyper-
calcaemia, and bradycardia, unless extreme, may be difficult to
detect at an age when the heart rate is so labile.

Idiopathic hypercalcaemia of infancy.

Some authors who have described cases of idiopathic hypercal-
caemia have referred to their electrocardiographic findings (Table IX).
In some patients the electrocardiogram has been regarded as normal,
but in others, all suffering from the severe form of the disease,
various abnormalities have been seen.

Lowe and his associates (1954) reported a "low marginal QTc" in
one electrocardiogram, a change which they accepted as being consist-
ent with hypercalcaemia.

Fanconi and Girardet (1952) gave the electrocardiographic
findings in one case.   The QT interval was accepted as being within
normal limits.   The P wave was tall and sharp in standard leads
I and II.   The T wave was reported as being of normal height, but
I regard its contour in leads II and V3 of the published electrocard-
iogram as unusual, and especially in lead V3 where its summit may be
described as a plateau.

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TABLE IX

Electrocardiographic findings reported in cases of idiopathic hypercalcaemia of infancy

Author	No. of Cases	ELECTROCARDIOGRAM					
		P	PR	T	ST	QTc	Other
Lowe et al. (1954)	1	−	−	−	−	"Low marginal	−
Fanconi et al. (1952)	1	Tall, sharp in I and II Negative in V1 Biphasic in V2	−	Normal (?) in standard leads Shallow −ve in V1, +ve in V2	−	0.42	−
Schlesinger et al. (1952)	1	−	−	−	Elevated	0.48	−
Dawson et al. (1954)	1	−	−	Prominent	Elevated	−	−
Fletcher (1957)	1	−	−	−	Depressed in V3, V6	0.475	−
Schwartz (1957)	1	−	Prolonged	−	−		Incomplete bundle branch block
Morgan el al. (1956)	1	−	Not prolonged	−	−	−	−
Creery & Neill (1954)	2	— REGARDED AS SHOWING NO ABNORMALITY —					
Lowe et al. (1954)	1	"	"	"	"	"	
Macdonald & Stapleton (1955)	1	"	"	"	"	"	
Rhaney & Mitchell (1956)	1	"	"	"	"	"	
Daeschner & Daeschner (1957)	1	"	"	"	"	"	
Kowarski (1958)	1	"	"	"	"	"	

In a patient examined by Schlesinger and his associates (1952) an electrocardiogram was recorded because of the presence of a systolic murmur before there was any other evidence of severe idiopathic hypercalcaemia.   This showed an elevated ST segment and a prolonged QT interval.   The electrocardiogram was thought to be suggestive of cretinism but the infant was not a cretin.   Twenty-six weeks later when the disease was fully developed the length of the QT interval was considered to be normal.

Dawson, Craig and Perera (1954) studied one patient and report-ed elevation of the ST segment in several leads and prominent T waves. Fletcher (1957) in a description of one case reported depression of the ST segment in two unipolar chest leads, and lengthening of the QT interval, but did not mention the character of the T waves. Again from a study of one case Schwartz (1957) reported an increase in the length of the PR interval and incomplete bundle branch block.

These descriptions of electrocardiograms in idiopathic hypercalcaemia are remarkable for three reasons.   First; some have been regarded as showing no abnormality in the presence of hypercal-caemia.   Second; the expected finding of a short QT interval has been only once reported, whereas an unduly long interval has been noted on two occasions.   Third; no uniformity is detectable among the abnormal findings.

The/

The present investigation was conducted against this background of uncertainty, but it still seemed possible that electrocardiography might supply sufficiently reliable information to permit this method of assessment of the serum calcium to replace chemical estimations during the treatment of patients with idiopathic hypercalcaemia.

MATERIAL AND METHODS

Hypercalcaemia induced with calcium gluconate

The electrocardiographic features of hypercalcaemia induced by the intravenous injection of calcium gluconate were studied. Three infants (Infants A, B and C) suffering from erythroblastosis foetalis were examined during the course of replacement transfusion with citrated whole blood before and after the injection of calcium gluconate through the umbilical vein. At the time of the replacement transfusion two (Infants A and C) were 17 hours old and the other (Infant B) was 52 hours old. Two (Infants A and B) were given 0.5 gram of calcium gluconate as a 10% solution, and the other (Infant C) 0.2 gram. Each injection was completed in the course of one minute. The standard limb leads were recorded at the beginning of the transfusion. The injection of calcium gluconate was given at that point during the transfusion at which electrocardiographic evidence of hypocalcaemia was though to be present.

In/

In infant A this was after 450 ml. of blood had been replaced, in infant B after 500 ml. and in infant C after 400 ml. The electrocardiogram was recorded immediately before the injection. The replacement transfusion was continued after the administration of the calcium salt and one minute later the electrocardiogram was again recorded. The calcium content of the serum at the time of each electrocardiographic examination was noted.

Idiopathic hypercalcaemia

Twenty-five patients suffering from idiopathic hypercalaemia were studied. Twenty-four of these were admitted to one medical unit at the Royal Hospital for Sick Children, Glasgow, during 1955 to 1957. At admission their ages ranged from 4 weeks to 22 months. In three cases another disease co-existed, namely hyperchloraemic renal acidosis in one, congenital toxoplasmosis in another and osteogenesis imperfecta in the third. With the exception of a single patient with the "severe" type of idiopathic hypercalcaemia and one other patient, each of whom had an apical systolic murmur, none had clinical evidence of heart disease (Table X).

Every patient showed at some point a serum calcium beyond the range encountered in healthy infants in the hospital, namely 10.1 to 11.5 mg. per 100 ml. The highest values of serum calcium found in individual patients varied from 12 to 18.6 mg. per 100 ml.

Every/

TABLE X

Data concerning 24 patients with idiopathic hypercalcaemia

Case No.	Age at Admission (Weeks)	Sex (M/F)	Daily Intake of Vitamin D at Onset of Symptoms (Internat. Units)	Highest Recorded Serum Calcium (mg./ 100 ml.)	Remarks
1	32	F	1120	16.6	
2	29	M	880	18.6	
3	60	M	700	13.4	
4	33	M	1716	15.3	
5	35	M	1316	18.0	
6	48	M	1120	15.7	
7	38	M	8840	14.0	
8	20	F	1450	13.9	
9	92	M	2800	15.3	"Severe" type
10	37	F	500	12.8	Hyperchloraemic renal acidosis
11	21	F	2200	13.0	
12	4	M	700	12.9	Toxoplasmosis
13	35	F	2700	15.8	
14	20	M	1500	12.0	
15	14	F	890	13.7	
16	36	M	1050	16.2	
17	61	M	3950	14.2	Systolic murmur
18	33	M	1866	13.8	
19	36	M	1050	14.6	
20	26	M	1680	14.5	Osteogenesis imperfecta
21	43	M	2036	15.6	
22	4	M	336	12.3	
23	35	M	700	12.3	
24	34	M	700	12.2	

Every patient had received vitamin D_2 as a prophylactic measure and the estimated daily intake of this vitamin at the onset of symptoms was from 336 to 8840 international units.   It was considered that these figures were reliable, but that estimates of the total intake since birth would be less accurate due to lapses of time and memory. Details of the intake of vitamin D and of individual serum calcium values are set out in Table X.

Electrocardiograms were recorded during a day on which the serum calcium was measured, but they were not obtained in every case at the time when the serum calcium was at its highest level.   The number of electrocardiographic examinations of individual patients varied from one to seven.   After one electrocardiogram had been recorded, further examinations were carried out only if the initial electrocardiogram seemed abnormal.   In two cases (Case Nos. 5 and 16) electrocardiograms were obtained at weekly intervals until the disease was considered to be cured on clinical and biochemical grounds.   Altogether 53 electrocardiograms were found to be of a quality adequate for critical scrutiny.

Statistical comparisons were made between the time intervals in these electrocardiograms and in those of healthy infants, and the scope of the analysis is outlined in Appendix II.   The healthy infants/

infants whose electrocardiograms were analysed in Part I of the
present investigations and which were used for comparison are
referred to as the control series.

The serum potassium was recorded in 14 patients, and the serum
cholesterol in 6 patients on the same day as that on which an
electrocardiogram was obtained. (The biochemical methods are
given in Appendix IX).

A more extensive electrocardiographic examination was made in
1959 of the twenty-fifth patient, a boy (K.M.) aged 8 months who
suffered from mild idiopathic hypercalcaemia. The unipolar
praecordial leads V4R, V1, V4 and V6 were recorded in addition
to the standard limb leads at weekly and later at fortnightly
intervals throughout his stay in hospital. Particular care was
taken to ensure that each electrocardiographic examination was
made immediately before the withdrawal of blood for the estimation
of serum calcium. These examinations were made to study in the
praecordial leads the location of electrocardiographic changes
and to eliminate any possible doubt as to the precise level of
serum calcium at the time of the electrocardiographic examinations.

<u>Other electrocardiographic</u>
<u>examinations</u>

For/

For comparison with electrocardiograms obtained in idiopathic hypercalcaemia, electrocardiographic examinations were made of two children with hypercholesterolaemia, of one with vitamin D poisoning and of four who were undergoing treatment with large doses of this vitamin.

HYPERCALCAEMIA INDUCED WITH CALCIUM GLUCONATE

Results

Heart rate.

In each instance the heart rate fell between the beginning of the replacement transfusion and the administration of calcium gluconate.   One minute after the injection the rate had fallen still further in two patients (Infants A and C) but remained unaltered in the other (Table XI).   In all patients however the total calcium content of the serum had more than doubled after the administration of the calcium salt.

TABLE XI/

TABLE XI

Replacement Transfusion: The effect of intravenous calcium gluconate on serum calcium concentration, heart rate and QT interval.

	Infant A	Infant B	Infant C
Before Transfusion Serum calcium (mg./ 100 ml. Heart rate (per minute) QT (seconds)	9.7 113 0.31	9.1 136 0.24	9.3 158 0.25
Before Calcium Gluconate Serum calcium (mg./ 100 ml.) Heart rate (per minute) QT (seconds)	8.9 77 0.36	8.95 103 0.30	9.3 133 0.29
After Calcium Gluconate Serum calcium (mg./ 100 ml.) Heart rate (per minute) QT (seconds)	22.9 67 0.29	18.8 103 0.28	19.8 111 0.30

QT interval

The QT interval of each patient lengthened before the injection of calcium gluconate. After the injection it shortened in two instances (Infants A and B) but became longer by 0.01 second in the infant (Infant C) who had received the smaller dose of calcium (Table XI). However when the interval was corrected to counteract the effect of heart rate it was found that the QTc value of each patient had decreased after the administration of calcium (Table XII).

TABLE XII/

TABLE XII

<u>Replacement Transfusion:</u> The effect of intravenous calcium
gluconate on serum calcium concentration and QTc.

	Infant A	Infant B	Infant C
Before Transfusion Serum calcium (mg./ 100 ml. QTc	9.7 0.425	9.1 0.36	9.3 0.405
Before Calcium Gluconate Serum calcium mg./ 100 ml.) QTc.	8.9 0.405	8.95 0.395	9.3 0.43
After Calcium Gluconate Serum calcium (mg./ 100 ml.) QTc	22.9 0.305	18.8 0.37	19.8 0.41

When the components of the QT interval were studied it was
found that the length of the ST segment of each patient had also
decreased after the administration of calcium gluconate, where-
as from the start of the transfusion until that point it had
lengthened (Table XIII).

TABLE XIII/

TABLE XIII

Replacement Transfusion: ST segment (seconds) before and after
intravenous calcium gluconate.

	Infant A	Infant B	Infant C
Before transfusion	0.11	0.08	0.07
Before calcium gluconate	0.19	0.12	0.10
After calcium gluconate	0.08	0.08	0.06

In contrast to the behaviour of the ST segment, the T wave
of each patient became longer after the administration of calcium
gluconate (Table XIV). In Infant C the lengthening of the T
wave more than offset the shortening of the ST segment and it was
for this reason that in this instance the measured QT interval
lengthened after the administration of calcium gluconate.

TABLE XIV

Replacement Transfusion: Length of T wave (seconds) before
and after intravenous calcium gluconate.

	Infant A	Infant B	Infant C
Before transfusion	0.20	0.16	0.18
Before calcium gluconate	0.17	0.18	0.19
After calcium gluconate	0.21	0.20	0.24

PR interval/

PR interval

The PR interval lengthened in two patients but shortened in the other (Infant C) after the injection of calcium gluconate (Table XV). In two patients it was longer in the last electrocardiogram than at the beginning of the transfusion but in the third patient it was of the same length.

TABLE XV

Replacement Transfusion: PR interval (seconds) before and after intravenous calcium gluconate

	Infant A	Infant B	Infant C
Before transfusion	0.10	0.09	0.10
Before calcium gluconate	0.10	0.10	0.11
After calcium gluconate	0.12	0.11	0.10

Arrhythmia

Sinus arrhythmia was the only disorder of heart rhythm observed. It occurred after the administration of calcium gluconate to Infants A and B but was not observed in Infant C who had been given the smaller dose.

Contour of the T wave

Reference must be made to the contour of the T wave because this will be shown to be of importance in idiopathic hypercalcaemia.

After/
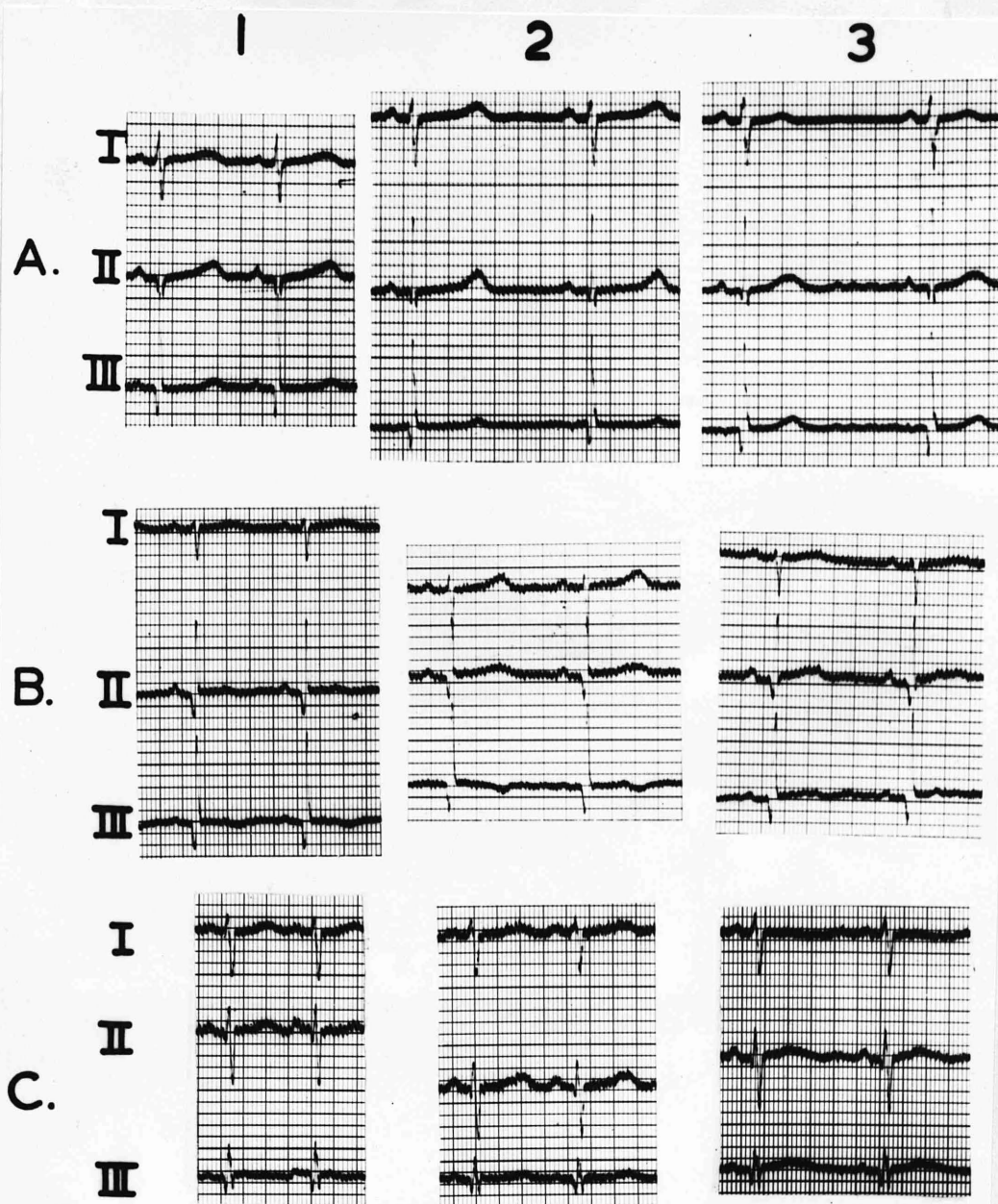
Fig. 3. <u>Induced hypercalcaemia</u>: Electrocardiograms from infants A, B and C. The first electrocardiogram of each series was obtained at the start of replacement transfusion, the second immediately before and the third one minute after the injection of calcium gluconate.

After the administration of calcium gluconate the T wave did not become taller or more prominent.   The waves lengthened but their summits did not form a plateau (Fig. 3).

D i s c u s s i o n

Firm conclusions cannot be derived from so few cases but certain trends are obvious.   With the appearance of hypercalcaemia the QT$_c$ value decreased and the ST segment shortened.   At the same time the T wave lengthened.   Lengthening of the T wave must be accepted with caution as a sign of hypercalcaemia because in this disorder slowing of the heart has been reported, and, as was shown in Part I, this may cause lengthening of the T wave.   If, on the other hand, slowing of the heart also leads to lengthening of the ST segment, and this too was shown in Part I, shortening of this segment is likely to be a more reliable sign of hypercalcaemia.

Slowing of the heart rate, lengthening of the PR interval and the appearance of sinus arrhythmia seemed to be less sensitive indices of hypercalcaemia, for each of these changes occurred in only two of the three patients.

IDIOPATHIC HYPERCALCAEMIA

R e s u l t s/
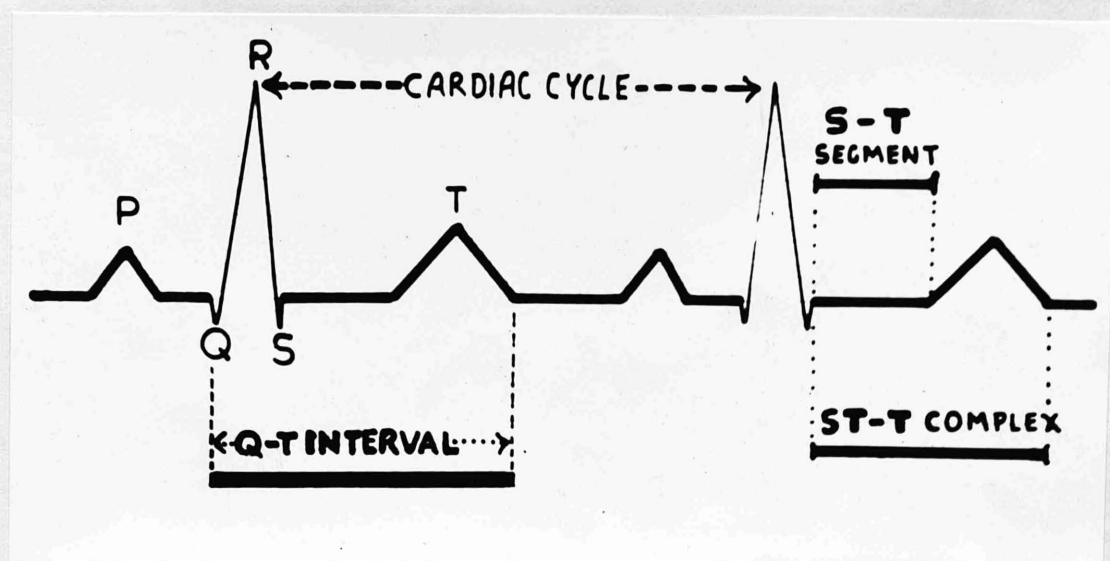
Fig. 4. Diagram showing the nomenclature used in describing the cardiac cycle in hypercalcaemia.

CASE NO

2 11 19

3 13 20

4 16

5 17 21

6 18 23
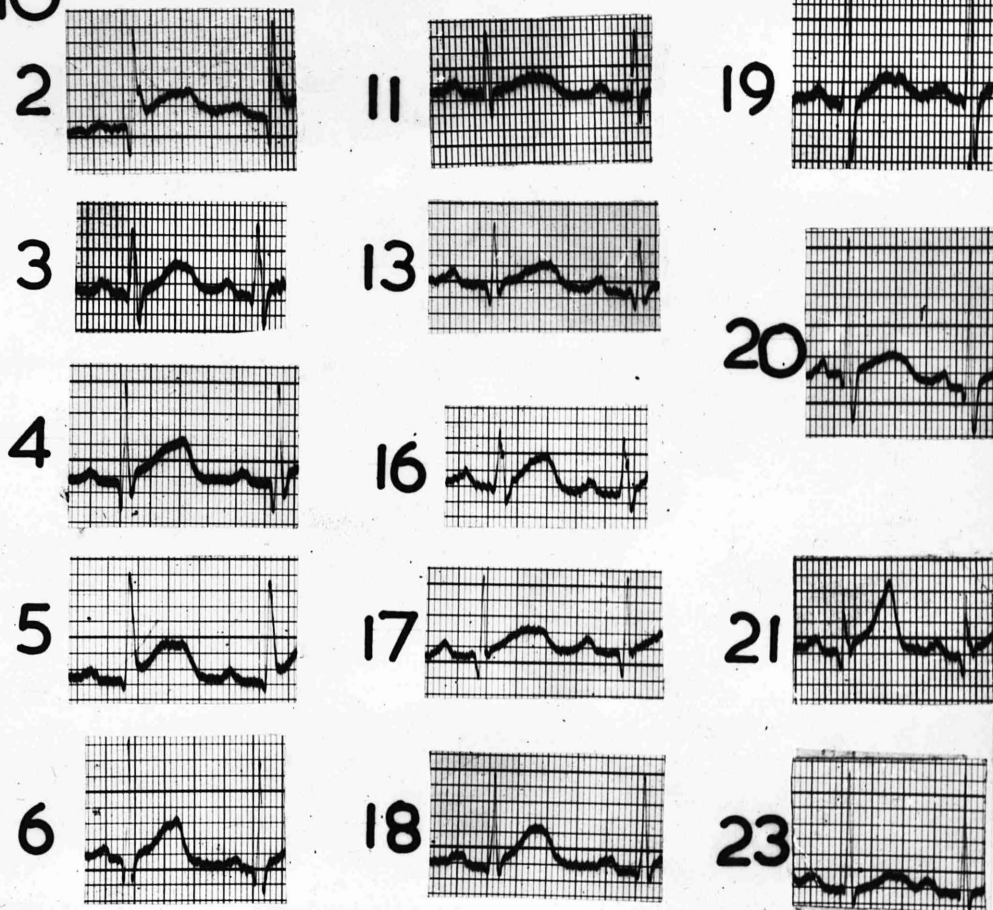
Fig. 5. Idiopathic hypercalcaemia: A portion of standard lead II taken from one electrocardiogram of each case which showed changes in the contour of the ST-T complex.

Case No.	Serum Calcium (mg./100 ml.)	Case No.	Serum Calcium (mg./100 ml.)
2	16.5	16	16.2
3	10.2	17	10.4
4	13.5	18	13.1
5	17.6	19	14.6
6	11.8	20	13.4
11	11.2	21	12.1
13	11.0	23	12.3
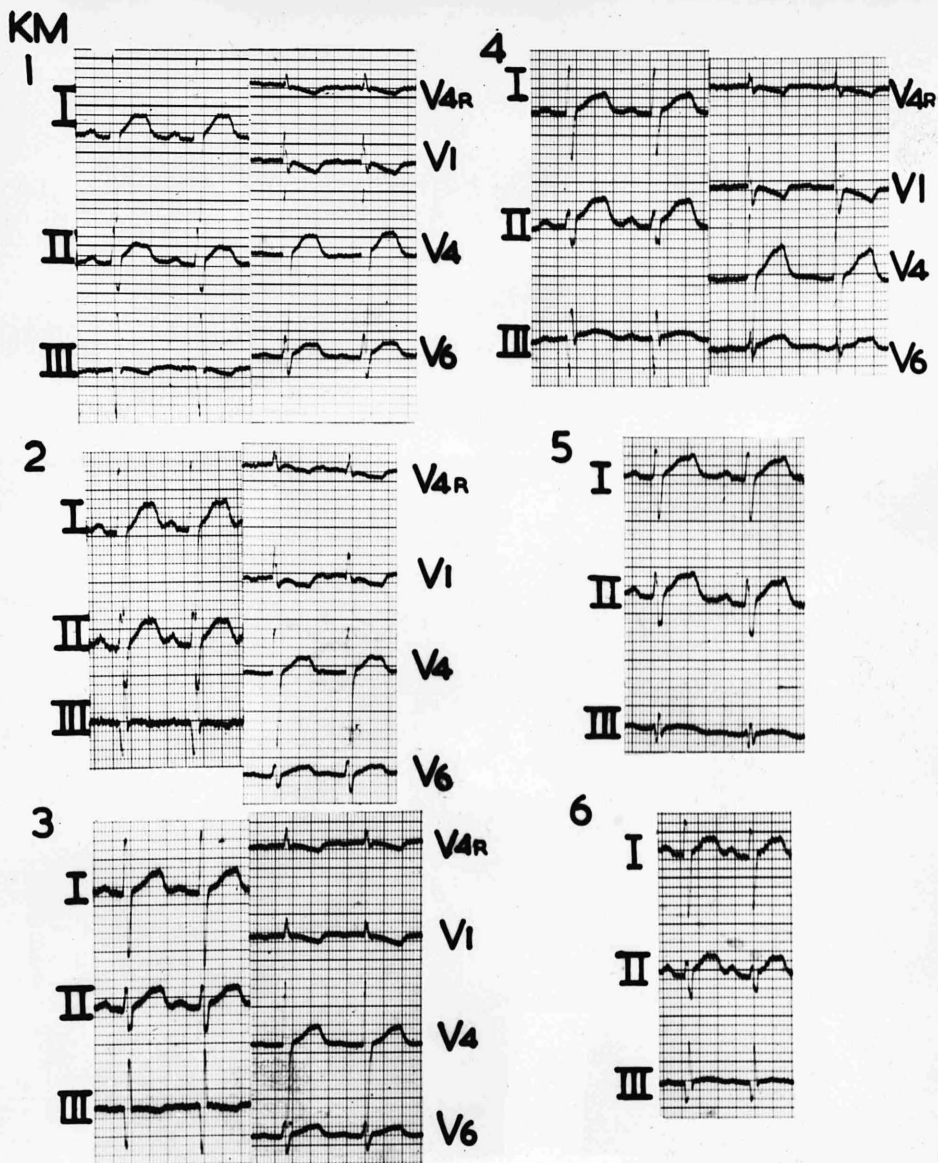
Fig. 6.   Idiopathic hypercalcaemia: Electrocardiograms
from patient K.M. showing abnormal contour of
ST-T complex, and its persistence 6 weeks after
hypercalcaemia has subsided.   The abnormal
contour of the complex is clearly seen in standard
leads I and II and in unipolar chest leads V4 and V6.

E.C.G.	Date	Serum calcium (mg./100 ml.)	QTc
1	10.11.59.	13.3	.39
2	17.11.59.	11.4	.425
3	24.11.59.	10.3	.415
4	1.12.59.	11.5	.395
5	15.12.59.	11.2	.395
6	29.12.59.	11.5	.385
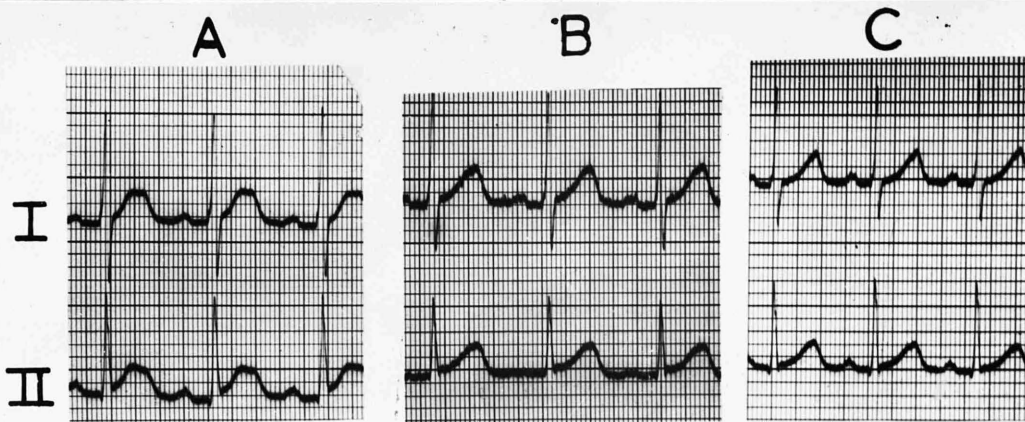
Fig. 7. Idiopathic hypercalcaemia: (Case No. 5.) Standard leads I and II showing regression of ST-T changes as hypercalcaemia subsides.

A.   ST elevation and plateau T wave.   QTc 0.39.
     Serum calcium 18 mg./100 ml.

B.   One week later.   ST elevation persists.   QTc
     0.405.   Serum calcium 11.3 mg./100 ml.

C.   Three weeks later.   Normal ST-T complex.
     QTc 0.37.   Serum calcium 10.9 mg./100 ml.
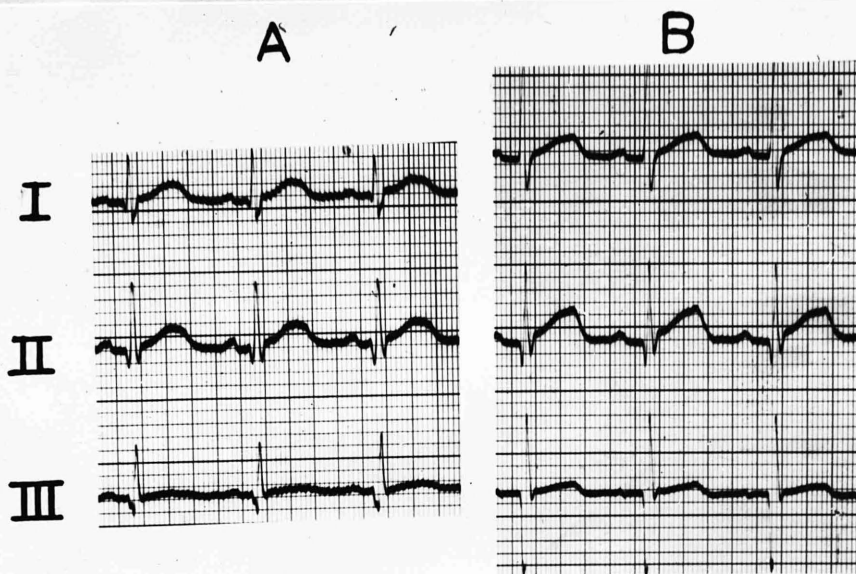
Fig. 8. Idiopathic hypercalcaemia: (Case No. 4.)   The abnormal contour of the ST-T complex is more marked in record B when the serum calcium had fallen to 13.5 mg./100 ml., than in record A obtained one week before when the serum calcium was 15.3 mg./100 ml.
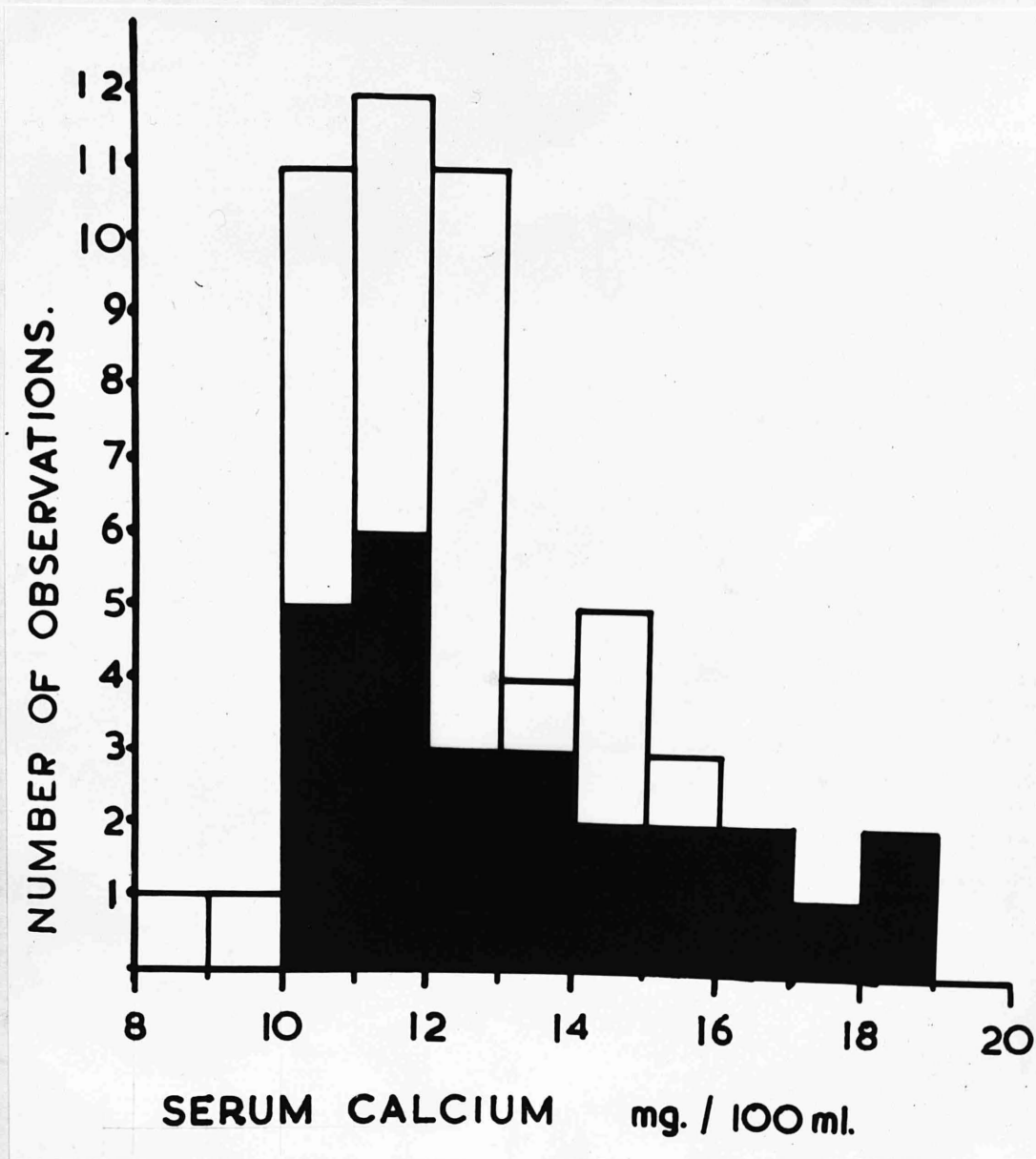
Fig. 9.   Idiopathic hypercalcaemia: Distribution of 53
          electrocardiograms related to the serum calcium.
          The black portion of each column represents
          electrocardiograms with changes in the contour
          of the ST-T complex.

TABLE XVI

Data concerning 24 patients with idiopathic hypercalcaemia

Case No.	Sex (M/F)	Highest Recorded Serum Calcium (mg./100 ml.)	Changes in Contour of ST-T Complex
1	F	16.6	Absent
2	M	18.6	Present
3	M	13.4	Present
4	M	15.3	Present
5	M	18.0	Present
6	M	15.7	Present
7	M	14.0	Absent
8	F	13.9	Absent
9	M	15.3	Absent
10	F	12.8	Absent
11	F	13.0	Present
12	M	12.9	Absent
13	F	15.8	Present
14	M	12.0	Absent
15	F	13.7	Absent
16	M	16.2	Present
17	M	14.2	Present
18	M	13.8	Present
19	M	14.6	Present
20	M	14.5	Present
21	M	15.6	Present
22	M	12.3	Absent
23	M	12.3	Present
24	M	12.2	Absent

IDIOPATHIC HYPERCALCAEMIA

R e s u l t s

ST-T Complex

Fourteen of 24 patients had a distinct abnormality in the contour of the electrocardiogram at some time during the course of the disease (Table XVI). Twenty-six of the 53 electrocardiograms analysed were abnormal.

The changes were best seen in standard leads I and II and were confined to the ST-T complex (Fig. 4). The ST segment was usually elevated and sometimes merged with the upward deflection of an unusually broad and prominent T wave. The summit of the T wave was flattened and formed a plateau which in a few instances was slightly notched (Fig. 5 and Appendix VIII). In one patient (Fig. 5, Case No. 21) the ST segment was elevated in lead II and the T wave in leads I and II was tall and pointed. In sharp contrast to the appearances of leads I and II was the virtual absence of change in the contour of lead III.

The twenty-fifth patient (K.M.) also had prominent, broad, flat-topped T waves in leads I and II but not in lead III (Fig. 6). Similarly abnormal T waves were found in the left praecordial leads V4 and V6, but not in the right praecordial leads, V4R and V1, in which the T waves were inverted and shallow. The difference in contour between the T waves in leads I and II and those in lead III

was/

was taken to be a reflection of the localization of the abnormal T
wave disclosed by the praecordial leads.

As a rule, the higher the serum calcium the more pronounced were
the changes (Fig. 7), but there were several striking exceptions to
this observation.   Not infrequently the change in contour persisted
even after the serum calcium had fallen to a normal level and in one
patient it became more pronounced as the hypercalcaemia was declining
(Fig. 8).   In 8 patients the ST-T complex was abnormal when the serum
calcium was within the normal range;   in 4 patients it was normal
when the serum calcium was highly elevated, and in 3 it returned to
normal while the serum calcium was still elevated (Fig. 9).   The
electrocardiograms of the patient K.M. showed the lack of correlation
between serum calcium level and the abnormal ST-T complex particular-
ly well;   the contour of the complex was still quite abnormal 6 weeks
after the serum calcium had fallen to within normal limits (Fig. 6).

For the further analysis of these electrocardiograms they were
divided into two groups, those in which there was an obvious change
in the contour of the ST-T complex and those in which there was none.
In order that comparisons might be made with electrocardiograms obtain-
ed from the control series of healthy infants it was necessary to omit
from the analysis seven electrocardiograms taken from three patients
who were more than a year old at the time of examination.
Forty-six/

Forty-six electrocardiograms remained and there were 23 in each group. The data used for analysis are set out in Appendix V.

Age and heart rate

The mean age pertaining to the electrocardiograms with no changes in contour was 31.6 weeks and this did not differ significantly from the mean of the control series. Neither was there a significant difference between the means of the two small groups (31.6 and 35 weeks). The mean age of the patients whose electrocardiograms showed the abnormal contour was, however, significantly greater than that of the controls (3.85 times the standard error of the difference between the means).

There was no significant difference between the mean heart rate of the control series and that of the electrocardiograms without changes in the contour of the ST-T complex (139.5/minute) nor was there a significant difference between the mean heart rate of the latter group and that of the group with changes in the contour of the ST-T complex (131.6/minute). The mean heart rate of the controls was however significantly greater than that of the electrocardiograms with changes in the ST-T complex (2.8 times the standard error of the difference between means), but when reference was made to the regression equation constructed for the control series to relate heart rate to age (Appendix IV), it did not seem necessary to invoke any factor/
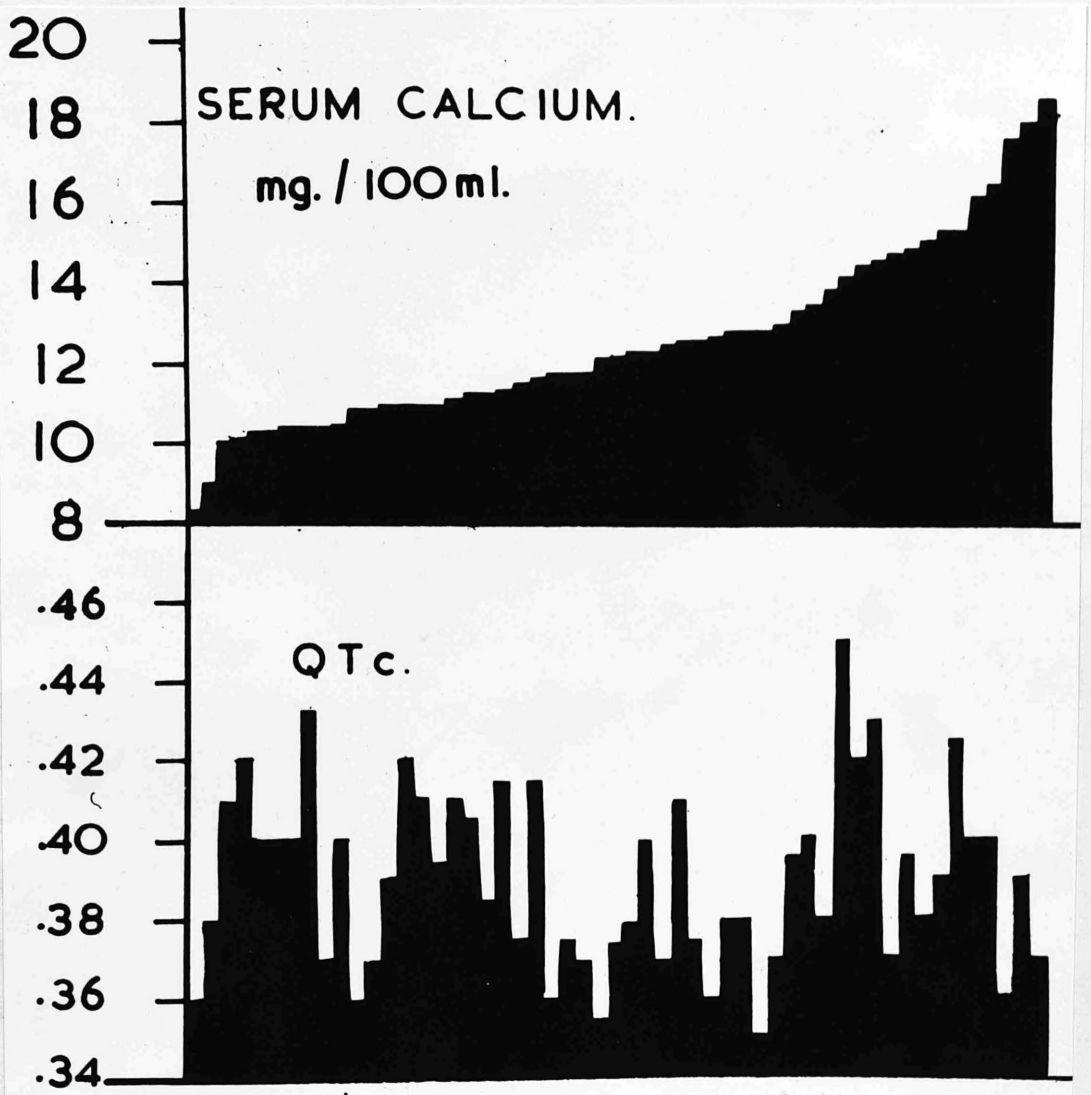
Fig. 10. <u>Idiopathic hypercalcaemia</u>: Correlation of the QTc values of 53 electrocardiograms with the prevailing level of serum calcium.

factor other than age to explain this difference.

QT interval and QTc

Shortening of the corrected QT interval (QTc), if not of the measured QT interval, was expected to occur in idiopathic hypercalcaemia just as it did in association with hypercalcaemia induced with calcium gluconate. However in this series the raised serum calcium was not accompanied by shortening of the QTc.

This lack of association between serum calcium and QTc can be illustrated in various ways. In Figure 10 the serum calcium levels corresponding to the 53 electrocardiograms are set out in order of increasing concentration and the 53 QTc values are correlated with them; the rising slope of serum calcium concentration is not reflected by a downward slope of QTc values. Thirty-three electrocardiograms were recorded while the serum calcium was elevated; in 27 of these the QTc value was within the range for infancy reported in Part I, in 4 it was above, and in only two instances was it below.

In order to confirm this apparent dissociation between QTc value and serum calcium statistical tests were applied (Appendices VI and VII). If the QTc values were indeed reflecting the serum calcium concentration the coefficient of correlation of QTc with serum calcium concentration would be negative and significant. The/

The coefficient (r) derived from 53 observations was +0.015 and this did not indicate that there was any significant correlation between the two measurements. The QT and the QTc values of the samples were then compared with those of the control series. Analyses of variance showed that the values of QT and QTc in the electrocardiograms of patients with idiopathic hypercalcaemia did not differ significantly from those in the electrocardiograms of the control series and that there was no significant difference in this respect between electrocardiograms with and without changes in the contour of the ST-T complex.

The discovery that the QTc values of patients with idiopathic hypercalcaemia did not reflect the level of serum calcium, and that their QT intervals and QTc values were no different from those likely to arise by chance within a population of healthy infants, led to a study of the three components of the QT interval, the ST segment, the T wave and the QRS complex.

ST segment.

Attention has already been drawn to the belief that the ST segment shortens in response to hypercalcaemia and this belief received support from the examination of the newborn infants whose hypercalcaemia was induced by the injection of calcium gluconate.

When the length of ST segments in 53 electrocardiograms was compared/

compared with the level of serum calcium the coefficient of correlation (r) was found to be -0.5924.   This negative correlation is very significant (p = <0.01) and implies shortening of the ST segment in relation to an increasing concentration of serum calcium.

The length of the ST segment in the two groups of electrocardiograms obtained from patients and in those from control subjects was subjected to an analysis of variance.   The mean values all differed significantly from each other (p = <0.01).   In electrocardiograms without changes in the contour of the ST-T complex the ST segment was significantly shorter than in the control series and it was even shorter in electrocardiograms which showed changes in the ST-T complex. The disparity in the length of the ST segment between the two groups of electrocardiograms of idiopathic hypercalcaemia may be explained by the finding that levels of serum calcium pertaining to the group with changes in contour were significantly greater than those pertaining to the other group (Difference in means = 2.9 times the standard error of the means).   Thus it has been shown that the ST segment shortened as the level of the serum calcium rose, but the failure of the QT interval and of the QTc value to behave in a similar fashion is so far unexplained.

T wave.

The abnormal contour of the T wave in some electrocardiograms has already been described, and a feature of the abnormal wave was its exceptional breadth.   It seemed possible that this broad T

wave/
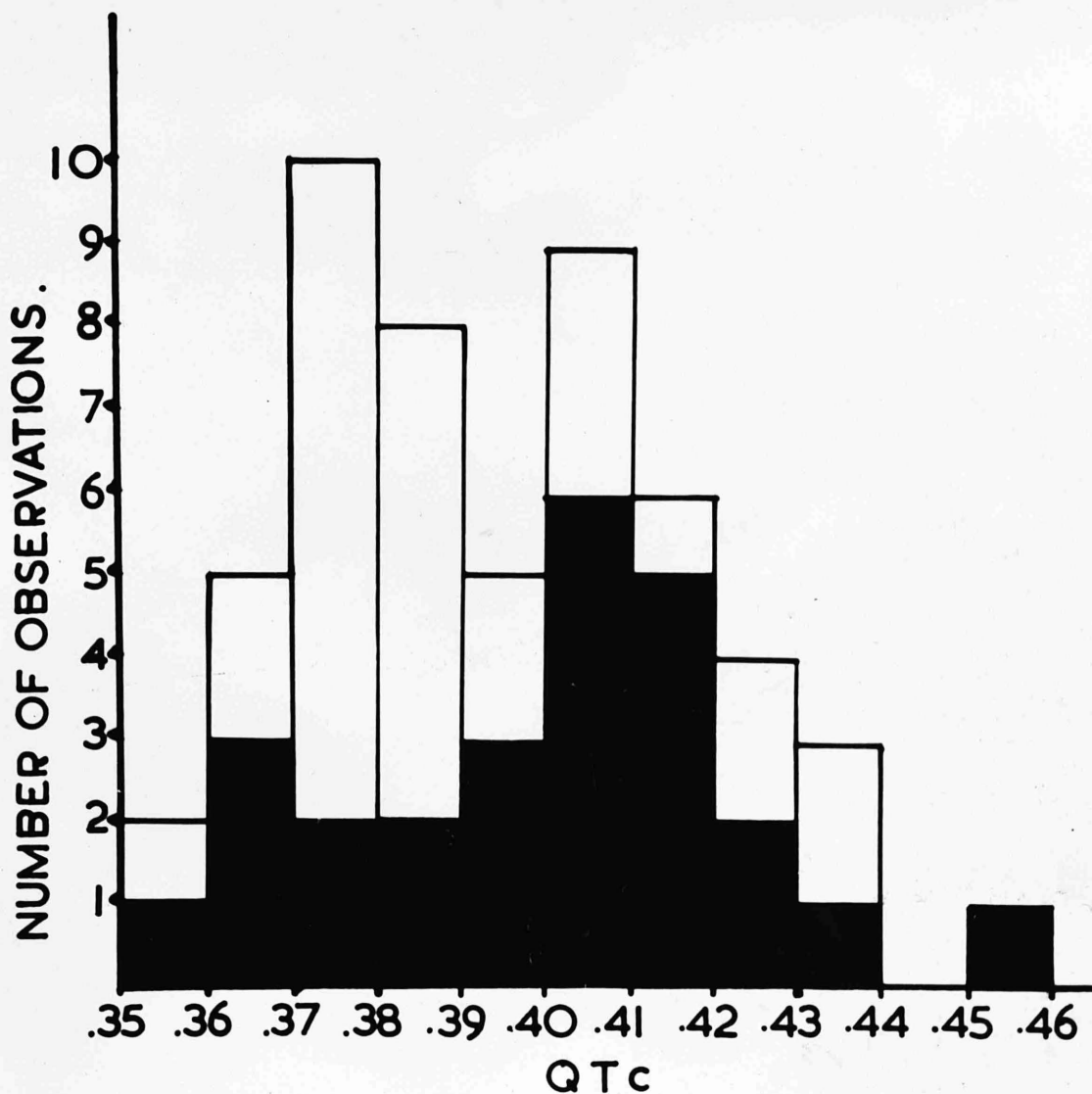
Fig. 11.   Idiopathic hypercalcaemia: Distribution of 53
electrocardiographic observations according to
QTc value.   The black portion of each column
represents electrocardiograms with changes in
the contour of the ST–T complex.

wave might prevent the QT interval (QTc) from shortening in response to hypercalcaemia but it would be necessary to explain why the QT interval (QTc) did not shorten even when the contour of the T wave did not seem abnormal. In Figure 11 the 53 electrocardiograms are divided into those with and those without changes in the contour of the T wave and are related to the value of QTc. This figure shows that, on the whole, electrocardiograms with changes in the contour of the T wave tended to have higher QTc values than those without changes in contour.

The length of the T wave in the 53 electrocardiograms was related to the serum calcium level and the coefficient of correlation was positive ($r = +0.3700$) and very significant ($p = <0.01$). This indicates that as the serum calcium concentration rose so the length of the T wave tended to increase.

The length of the T wave in the 23 electrocardiograms with changes in the contour of ST-T complex, in the 23 without changes in contour and in those of the control series was then subjected to an analysis of variance. Not only was the length of the T wave in electrocardiograms without changes in the contour of the ST-T complex significantly greater than in the control group, but in electrocardiograms with changes in the contour of the ST-T complex it was significantly greater than that in the group without changes ($p = <0.01$).

This/

This analysis suggests a close association between lengthening of the T wave and hypercalcaemia and this finding might afford an explanation for the failure of the QT interval to shorten in response to hypercalcaemia.

QRS complex.

The QRS complex is the last part of the QT interval to be considered.   In this instance there were no significant differences between its length in electrocardiograms of the control series and in those of patients with idiopathic hypercalcaemia.

PR interval

The length of the PR interval in the electrocardiograms without changes in the contour of the ST-T complex did not differ significantly from that in the control series, but in those with changes in the contour of the ST-T complex it was very significantly longer than in the other groups ($p = < 0.01$).   The meaning of this finding is not clear.   The length of the PR interval has been shown to be affected by both heart rate and age (Part I), but there was no significant difference in mean heart rate and mean age pertaining to the two groups of electrocardiograms from patients with idiopathic hypercalcaemia.

Hypercalcaemia has been said to cause lengthening of the PR interval and this was indeed observed by me in 2 of the 3 newborn infants/

infants after the injection of calcium gluconate.   In idiopathic
hypercalcaemia the mean calcium level associated with electrocard-
iograms with an abnormal ST-T contour was higher than that associated
with the electrocardiograms with a normal ST-T contour, and this
might explain why the mean PR interval of the former group, but not
of the latter group, was significantly longer than in the control
series.

P wave

The length of the P wave in electrocardiograms of patients with
idiopathic hypercalcaemia did not differ significantly from that in
the control series.

Configuration of P wave and QRS complex

The contour of the P wave and the configuration of the QRS
complex in the electrocardiograms of patients were not materially
different from those features in the electrocardiograms of the control
subjects.

Arrhythmia

Cardiac arrhythmia has been reported in association with hyper-
calcaemia.   The first of three electrocardiograms of one patient
(Case No. 11) showed occasional ventricular premature systoles but
the serum calcium at the time (10.1 mg. per 100 ml.) was within the
normal range.

No/

TABLE XVII

Idiopathic Hypercalcaemia. Serum potassium concentration
and electrocardiographic data (20 observations of 14 cases)

Case No.	Serum Potassium (m.Eq./litre	Changes in ST–T Contour	QTc
1	4.1	Absent	0.38
2	4.4 5.4 4.6	Present Present Absent	0.40 0.37 0.36
5	5.3 5.1	Present Present	0.36 0.38
9	4.7	Absent	0.425
10	4.2 5.9	Absent Absent	0.35 0.36
11	4.4 7.1 5.0	Present Present Absent	0.41 0.41 0.39
12	5.9	Absent	0.375
13	5.0	Absent	0.38
14	5.6	Absent	0.375
15	5.5	Absent	0.37
17	5.3	Absent	0.43
18	4.5	Present	0.37
19	4.2	Present	0.43
22	6.2	Absent	0.395

TABLE XVIII

Idiopathic Hypercalcaemia. Serum calcium and serum total
cholesterol concentration related to electrocardiographic
data in 13 observations of 6 cases

Case No.		3	8	16							17	19		22
Serum Calcium (mg./100 ml.)		10.2	13.9	16.2	11.0	12.6	12.6	10.3	10.4	12.3	12.2	14.6	11.7	11.1
Serum Total Cholesterol (mg./100 ml.)		248	336	276	331	235	192	219	190	200	400	260	211	214
E	QTc	.42	.38	.40	.41	.41	.375	.40	.435	.40	.43	.43	.415	.395
C G	Changes in ST-T contour*	P	A	P	P	P	A	A	A	A	A	P	A	A

* P = Present
  A = Absent

No other disturbance of cardiac rhythm occurred apart from small differences in the length of cardiac cycles which were never great enough to justify a diagnosis of sinus arrhythmia as defined by Krumbhaar and Jenks (1916). Thirty-six of 46 electrocardiograms showed these small amounts of variation, 17 of the 23 with changes in the contour of the ST-T complex and 19 of the 23 without changes in contour. This finding seems unlikely to have any particular relevance to the electrocardiography of idiopathic hypercalcaemia since similar amounts of variation in the length of cardiac cycles occurred frequently among the control subjects (Part I).

Serum potassium and serum cholesterol

There was no obvious association between changes in the contour of the ST-T complex and the levels of serum potassium (Table XVII) or of serum cholesterol (Table XVIII).

D i s c u s s i o n

We should first consider to what extent the electrocardiographic features of idiopathic hypercalcaemia are similar to and to what extent they differ from the accepted signs of hypercalcaemia.

QT interval and its components

Shortening of the corrected QT interval (QTc) which is the most widely accepted and most easily measured index of hypercalcaemia was not/

not a feature of these electrocardiograms. This finding is in agreement with those of Fanconi and Girardet (1952), Schlesinger, Butler and Black (1952) and Fletcher (1957) in three cases of severe idiopathic hypercalcaemia.

It has been shown however that the ST segment was shorter than in healthy infants and that shortening accompanied a rising level of serum calcium. On the other hand the T wave was found to be longer than in the electrocardiograms of healthy infants and there was a statistical association between lengthening of the T wave and a rising level of serum calcium. Lengthening of the T wave was considered to account for the failure of both the measured QT interval and the corrected QT interval (QTc) to shorten. Shortening of the ST segment is an accepted response to hypercalcaemia but lengthening of the T wave is not, although both changes occurred in the electrocardiograms of the newborn infants with induced hypercalcaemia. From the investigation of the control subjects it was concluded that the T wave tended to lengthen as the heart rate fell but in one of the newborn infants treated with calcium gluconate and in the patients with idiopathic hypercalcaemia the lengthening of the T wave cannot be attributed to the effect of heart rate. An association therefore exists between the length of the T wave and the level of serum calcium in patients with idiopathic hypercalcaemia but clearly this does not prove that lengthening is caused by hypercalcaemia. Indeed doubt must be cast on a true cause and effect relationship between the two

because/

because lengthening of the T wave of a degree sufficient to prevent shortening of the QT interval in hypercalcaemia cannot have been found by those observers who have established shortening of the QT interval as characteristic of hypercalcaemia. Moreover, while the T wave lengthened in the newborn infants given calcium gluconate this lengthening was not great enough to prevent the QTc value from decreasing.

It cannot be argued that lengthening of the T wave was indicative of a particularly severe degree of hypercalcaemia, for some of the other and perhaps more severe effects of hypercalcaemia, mentioned earlier, were absent.

PR interval

An unduly long PR interval indicative of delayed atrio-ventricular conduction has been reported as one of the electrocard-iographic signs of hypercalcaemia. The PR interval in electrocard-iograms with changes in the contour of the ST-T complex was signifi-cantly longer than in electrocardiograms with a normal contour. There was however no significant difference in the length of the PR interval between the latter group and the control series, and for this reason it is not altogether certain that the longer PR interval of the electrocardiograms with changes in the contour of the ST-T complex was merely a reflection of hypercalcaemia.

The contour of the ST-T complex

It/

It remains to be considered whether the observed abnormalities in the contour of the ST-T complex can be directly related to the serum calcium level. Changes in the contour of the ST-T complex were on the whole more prominent in those children with the highest serum calcium values, but the contour was sometimes within normal limits when the serum calcium was highly elevated, and abnormal when the serum calcium was within the normal range.

It is obvious that the changes in contour of the ST-T complex found in this series (elevation of the ST segment and a prominent T wave with a broad and flattened summit) are neither those usually attributed to the effect of hypercalcaemia, nor indeed do they appear to be directly related to the level of the serum calcium. One is led therefore to search for some other factor associated with idiopathic hypercalcaemia which could be responsible for this electrocardiographic picture. It is interesting at this point to recall that the electrocardiograms from patients with severe idiopathic hypercalcaemia described by Fanconi and Girardet (1952) and by Dawson and his colleagues (1954) showed exceptionally prominent T waves.

Hyperkalaemia

Hyperkalaemia may be responsible for the production of prominent T waves, (Page 191), but this metabolic disturbance is not a reported feature of idiopathic hypercalcaemia nor are the abnormal T waves in this series, with one exception (Case No. 21), similar to those of potassium intoxication. Moreover no association appears

to/

to exist between the serum potassium values and the presence or absence of changes in the contour of the ST-T complex.

Hypercholesterolaemia

Hypercholesterolaemia is a feature of idiopathic hypercalcaemia (Forfar et al. 1956), and it is therefore prudent to consider whether this might be the cause of the electrocardiographic changes. Bernasconi and Raynaud (1953) decided that hypercholesterolaemia was reflected in the electrocardiogram by lengthening of the QT interval and by T waves of low voltage; these T waves bear no resemblance to those encountered in idiopathic hypercalcaemia. Their description of the electrocardiogram in hypercholesterolaemia should however be accepted with reserve because the patient they studied was almost certainly suffering from hypothyroidism, and hypothyroidism is known to produce electrocardiographic changes which Schlesinger and Landtman (1949) considered to be the expression of the direct effect of thyroid hormone deficiency on the myocardium.

From the information available the correlation between the level of serum cholesterol and changes in the ST-T complex was no more satisfactory than between those changes and the serum calcium.

To explore further the possibility that hypercholesterolaemia might have a direct bearing on the contour of the ST-T complex two children with severe hypercholesterolaemia were examined. Both suffered from nephrosis. One was a boy (W.S.) aged 11 years whose/

WS

I

II

III

J Go.

I

II

III
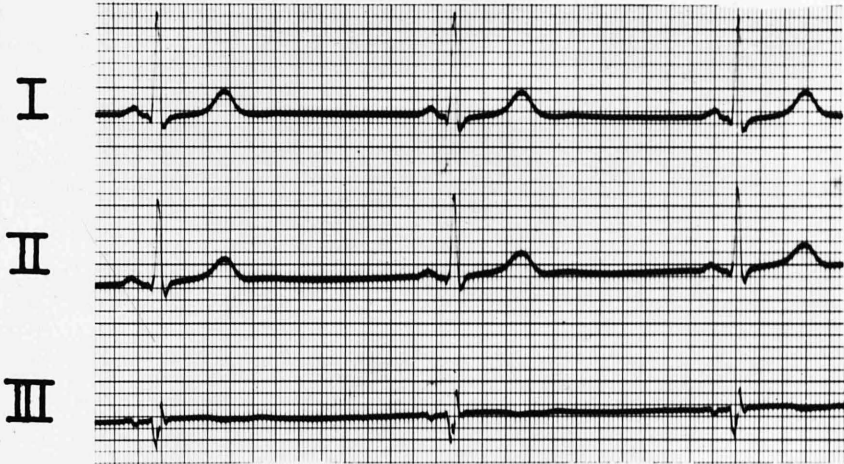
Fig. 12.   Hypercholesterolaemia: Electrocardiograms of
patients W.S. and J.Go. show no abnormality in
the contour of the ST-T complex.   Serum total
cholesterol 600 mg./100 ml. and 409 mg./100 ml.,
respectively.

whose serum total cholesterol was 600 mg./100 ml. and the other a
girl (J.Go.) aged 5 years whose serum total cholesterol was 409 mg./
100 ml. (upper limit of normal 250 mg./100 ml. by the method of
Zlatkis, Zak and Boyle 1953). In neither case did the electrocard-
iogram show any abnormality in the contour of the ST-T complex
(Fig. 12).

Vitamin D

Continuing the search for the cause of the electrocardiographic
changes in idiopathic hypercalcaemia, attention is now directed to the
influence of vitamin D on the electrocardiogram. This is done because
of the postulated connexion between this vitamin and the pathogenesis
of the disease. Ingestion of vitamin D, either as cod-liver oil (D_3)
or as one of the synthetic preparations (D_2), is known to produce
certain abnormalities in the electrocardiogram apart from those which
could be directly attributed to an associated hypercalcaemia.

Agdhur and Stenström (1929-31) studied electrocardiograms of mice,
rats, dogs, rabbits, pigs and calves treated with cod-liver oil.
Of particular interest is their discovery that in rabbits the summit
of the T wave sometimes became a plateau, and that the QT interval
lengthened simultaneously. In other animals, elevation of the ST
segment, lengthening of the QT interval, changes in the contour of
the T wave and a lengthened PR interval were observed.

About the same time Jundell and Stenström (1931) examined
infants/

infants treated for several weeks with cod-liver oil or Vigantol

(vitamin D_2) and found lengthened PR intervals, widened QRS complexes

and abnormal T waves.   In 1935 Uhse reported that the electrocard-

iograms of 54 out of a total of 65 children showed changes after

the administration of cod-liver oil (vitamin D_3) or Viosterol

(vitamin D_2) either alone or in combination.   These changes occurred

most frequently under the age of two years and persisted in some

instances for as long as 9 months.   They consisted of a shortened

ST segment with a broadened notched T wave.   There is a similarity

between his published electrocardiograms and that of Case No. 21 of

the present series.

In contrast, Anning and his associates (1948) found no constant

electrocardiographic signs which could be attributed to the adminis-

tration of calciferol (vitamin D_2), although they admitted that the

PR interval was sometimes lengthened and the QT interval (QTc)

shortened.   This study however was of adults aged from 42 to 66

years.

Electrocardiographic changes closely resembling those described

in this series have been recorded in patients suffering from vitamin

D poisoning, by Jelke (1946), by Skatvedt (1947) and by Hjelt and

his associates (1956).

Jelke's case, a girl of 17 months, had received 6.25 million

international/

international units of vitamin D_2 for the treatment of rickets.
The T wave was prominent, broad and flat-topped, the ST segment was
raised, but the QT interval was shortened.   When these observations
were made the serum calcium was 15.9 mg. per 100 ml.   The ST segment
remained elevated even after the serum calcium had fallen to normal.

Skatvedt's patient, a girl aged one year, had been given in
error 6.5 million international units of vitamin D_2 over a period
of 9 months.   On admission to hospital the serum calcium was
19.8 mg. per 100 ml.   There was elevation of the ST segment and a
marked platform (sic) T wave which was still abnormal three months
later although the child was well and the serum calcium was normal
in amount.   The QTc calculated from the published electrocardiograms
was not shortened.

Hjelt, Tähkä and Hallman (1956) described a child aged one year
who from birth had received 2 million international units of vitamin
D_2, of which 1.5 million units had been given during a period of four
months immediately preceding admission to hospital.   The serum
calcium was 15.6 mg. per 100 ml., and the published electrocardio-
gram (lead I) showed a broad, flat-topped T wave without shortening
of the QT interval (QTc).   This patient died three months later.
In an earlier paper these authors (Hallman, Hjelt and Tähkä 1954)
referred to the electrocardiogram of this patient and of four others
suffering/

suffering from vitamin D intoxication, and stated that both the

P and T waves were high (sic).

I have had the opportunity of studying one case of vitamin D

poisoning.   A girl aged $2\frac{1}{2}$ years was given 5.4 million international

units of vitamin D_2 over a period of five weeks immediately before

admission to hospital.   On admission the serum calcium was 19.6 mg.

per 100 ml., and the electrocardiogram showed elevation of the ST

segment in lead I and a broad, plateau T wave in leads I and II

(Fig. 13).   These abnormalities became less pronounced as the

hypercalcaemia subsided, but had not entirely disappeared when the

serum calcium returned to normal.   The QTc value was not at any time

below the normal range.   Hypercholesterolaemia accompanied the

hypercalcaemia, the highest recorded level of total cholesterol in

the serum being 500 mg./100 ml.

The association of these electrocardiographic signs with vitamin

D poisoning encouraged speculation as to the possibility of such

signs occurring in patients receiving large doses of vitamin D but

showing no clinical evidence of poisoning.

Four patients with late rickets were studied before and after

a course of vitamin D given by mouth (Fig. 14).   None developed

hypercalcaemia or any clinical sign of vitamin D intoxication.

J.R./
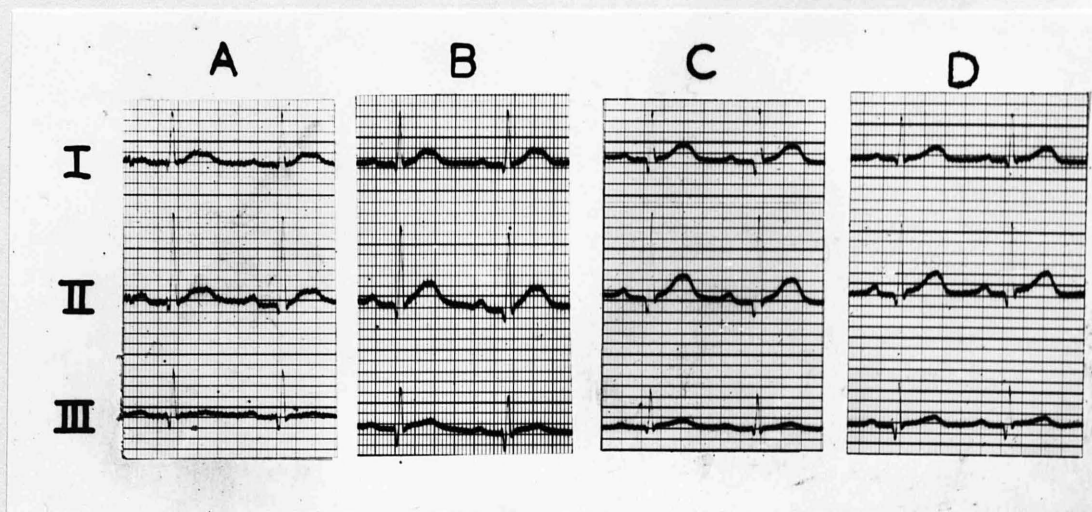
Fig. 13.   Vitamin D poisoning:

A.   On admission.   Plateau T wave (leads I and II)
      QTc 0.40.   Serum calcium 19.6 mg./100 ml.

B.   Three days later.   Plateau T wave (leads I and
      II).   ST elevation (lead II).   QTc 0.35.
      Serum calcium 15.6 mg./100 ml.

C.   Six days later.   Slight regression of changes
      in ST-T contour.   QTc 0.355.   Serum calcium
      12.5 mg./100 ml.

D.   Eighteen days later.   Further improvement in
      appearance of ST-T contour.   QTc 0.36.
      Serum calcium 10.7 mg./100 ml.
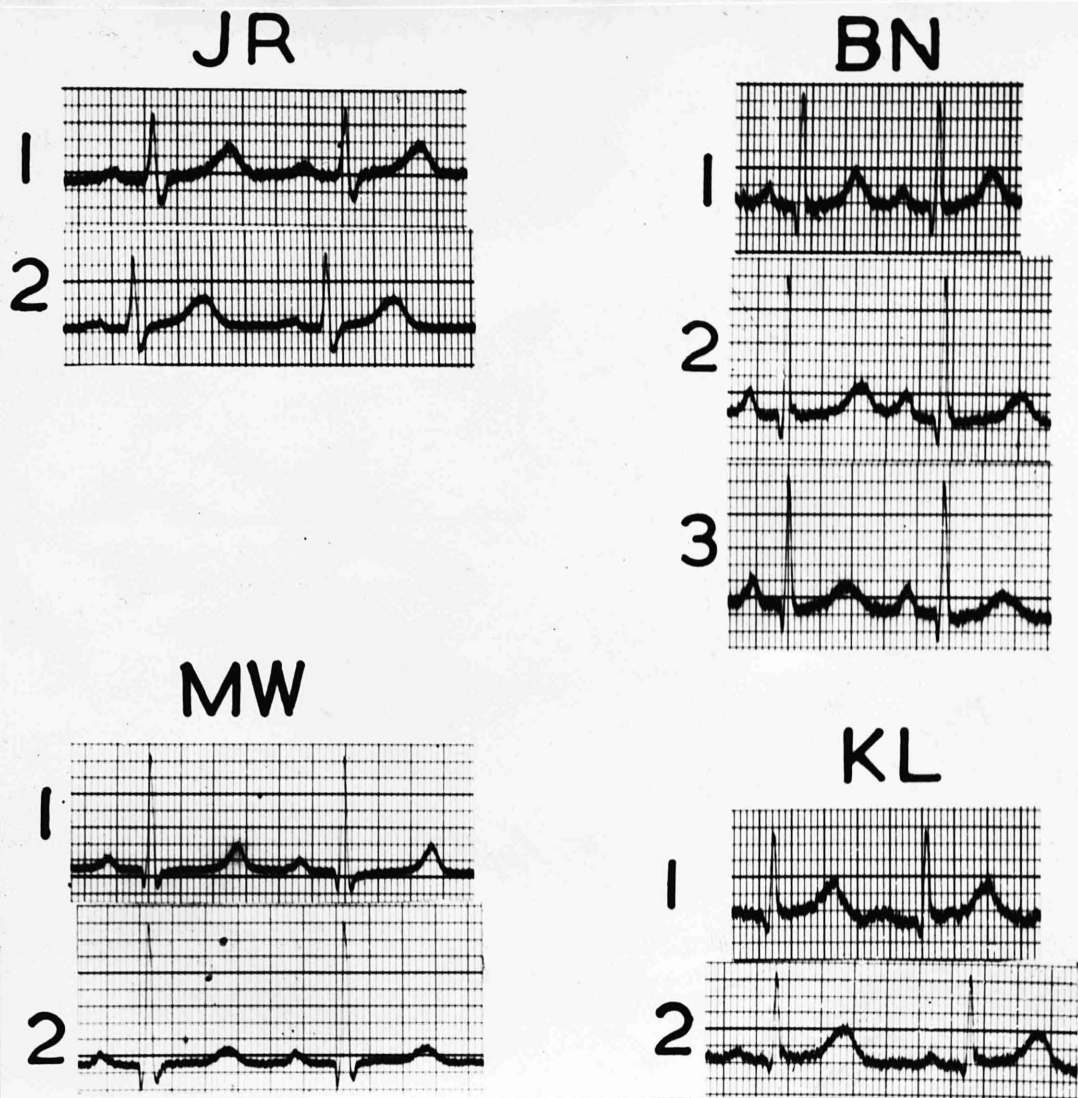
Fig. 14. <u>Vitamin D in late rickets:</u> Illustrations from standard lead II.

J.R. (coeliac rickets). Record 1 before and record 2 after 60,000 units vitamin D2 given over 60 days.

M.W. (renal rickets). Record 1 before and record 2 a fortnight after one dose of 600,000 units vitamin D2.

B.N. (Fanconi syndrome). Record 1 before two doses of vitamin D2 (600,000 and 700,000 units). Record 2 one week and record 3 two weeks after second dose.

K.L. (vitamin-D-resistent rickets). Record 1 before and record 2 after 10 million units vitamin D2 in 100 days.

In each case there is slight flattening of the T wave summit after vitamin D. Hypercalcaemia was not found in any case.

J.R. was five years old and suffered from coeliac rickets.
She was given 60,000 international units of vitamin D_2 over a
period of 60 days.   The only electrocardiographic change was
slight flattening of the peak of the T wave in leads I and II.

M.W., an eight-year-old girl who suffered from renal rickets,
was given a single dose of 600,000 units of vitamin D_2.   One week
later there had been no change in the electrocardiogram.   After
two weeks the peak of the T wave in leads I and II was slightly
flattened, and the T wave in lead III was inverted.   The QTc was
prolonged throughout, which may have been attributable to
persistent hypocalcaemia.   No other substantial alteration in the
ionic balance of the plasma was detected during the period of
observation.

B.N. aged 7 years had rickets as one manifestation of the
de Toni-Fanconi syndrome.   She was given 600,000 international
units of vitamin D_2 and three weeks later a further dose of
700,000 units.   No notable change in the electrocardiogram occur-
red until one week after the second dose of vitamin D, when the QTc
became prolonged (0.475) and the peak of the T waves in leads I and
II slightly depressed.   As in the previous case, a constant but
mild degree of hypocalcaemia was present throughout.   There was
no other important change in the chemistry of the plasma.

K.L. aged 6 years suffered from vitamin D resistent rickets.
Healing of the bony lesions was achieved by the administration of
10 million international units of vitamin D_2 over a period of 100
days.   Slight flattening of the peak of the T wave occurred but
this was no more pronounced than in the three patients who had
received smaller doses of vitamin D.

The/

The electrocardiographic changes described in these four patients were minimal, and were only obvious when a comparison was made of the records obtained before and after treatment. There is at least the suggestion however that the administration of vitamin D may in some way affect the contour of the T wave even in the absence of hypercalcaemia. The discrepancy between the large dose of vitamin D (10 million units) given to the patient (K.L.) suffering from vitamin D resistent rickets and the paucity of electrocardiographic effect could be taken to suggest that his resistance to vitamin D extended to actions of the vitamin beyond those concerned with ossification.

It would appear that the changes found in the electrocardiogram of infants with idiopathic hypercalcaemia are more likely to be related to the intake of vitamin D than directly to the hypercalcaemia. Lest it be thought that these electrocardiographic changes bore a quantitative relationship to the intake of vitamin D two observations should be made. The presence or absence of an abnormal contour of the ST-T complex seemed little related to the precise intake of vitamin D at the onset of symptoms (Table XIX), and the electrocardiographic abnormality appeared in several instances to be at least as great in patients with idiopathic hypercalcaemia as in patients with/

TABLE XIX

Data concerning 24 patients with idiopathic
hypercalcaemia

Case No.	Age at Admission (weeks)	Daily Intake of Vitamin D at Onset of Symptoms (Internat. Units)	Changes in Contour of ST-T Complex
1	32	1120	Absent
2	29	880	Present
3	60	700	Present
4	33	1716	Present
5	35	1316	Present
6	48	1120	Present
7	38	8840	Absent
8	20	1450	Absent
9	92	2800	Absent
10	37	500	Absent
11	21	2200	Present
12	4	700	Absent
13	35	2700	Present
14	20	1500	Absent
15	14	890	Absent
16	36	1050	Present
17	61	3950	Present
18	33	1866	Present
19	36	1050	Present
20	26	1680	Present
21	43	2036	Present
22	4	336	Absent
23	35	700	Present
24	34	700	Absent

with vitamin D poisoning who had been in receipt of much larger doses of vitamin D. Whether the synthetic vitamin D_2, containing, as it may, toxic products of irradiated ergosterol (Bicknell and Prescott 1942), is more prone to produce these changes than the natural vitamin D_3 is uncertain. Nevertheless these electrocardiographic findings lend further support to the idea that the administration of vitamin D is associated in some way with the onset of idiopathic hypercalcaemia of infancy.

The cause of the abnormal ST-T contour

It seems probable that the abnormal ST-T complex in idiopathic hypercalcaemia and in vitamin D poisoning can result from one of only two causes. It is an expression either of some chemical influence on the myocardium or of an organic disorder of the heart.

Sagall, Horn and Riseman (1943) used quinidine to produce changes in the ST-T complex similar to those found in the present series, but these changes disappeared within a few hours. They considered the changes to be an expression of the effect of quinidine on the refractory period of the ventricular muscle causing delayed repolarization. The changes in the present series are however characterised by their persistence for days or weeks. If indeed they are the manifestation of some chemical influence on the myocardium that influence must persist even after hypercalcaemia has subsided. I cannot regard this as impossible but it is difficult to imagine what chemical/

chemical disturbance could cause these persistent changes, and it would be unwise to presume that this is the explanation.

It is therefore pertinent to consider the evidence which might support the contention that the abnormal contour of the ST-T complex in idiopathic hypercalcaemia and in vitamin D poisoning is caused by an organic disorder of the heart. The type of disorder envisaged is either a primary lesion of the myocardium, or a coronary artery lesion causing ischaemia of the myocardium. Dressler, Roesler and Lackner (1951) were of the opinion that a notched or plateau T wave was suggestive of myocardial damage, and found that notching of T waves in the standard limb leads was often seen in patients with coronary arteriosclerosis. I should recall that the prominent plateau T wave in idiopathic hypercalcaemia was peculiarly localized to standard leads I and II and, in the patient whose praecordial leads were examined, to the leads V4 and V6. These leads are likely to give evidence of lesions of the left ventricular myocardium, but it is to be emphasized that the electrocardiographic changes were not those usually associated with infarction of the anterior myocardium (Katz 1946).

"It seems not impossible that cod-liver oil treatment in man may cause a chronic heart disease". This statement was made by Agduhr and Stenström (1930a) after their study of the electrocardiography and pathology of animals treated with cod-liver oil. Degenerative changes/

changes and calcification in the myocardium were regular findings
at autopsy in this experimental material.

Organic changes in the myocardium attributed to the consumption
of cod-liver oil (vitamin D_3) were reported by Malmberg (1928) in
two premature infants who died at the age of 16 days and 4 months.
In each case there was atrophy of muscle cells and connective tissue
change.   Ross and Williams (1939) found calcium deposition in the
media of arteries and in the myocardium of an infant who had suffered
from irradiated ergosterol (vitamin D_2) poisoning.   Debré (1948)
reported the deposition of calcium in the myocardium of a child aged
20 months who had suffered from vitamin D_2 poisoning after the
administration of 1,200,000 international units.   An extreme example
of this kind (Bauer and Freyberg 1946) concerned a young adult who had
consumed huge quantities of vitamin D in the year before her death.
In the coronary arteries there was thickening of the intima and
calcification of the media;   in the myocardium fatty change and
areas of infarction were found.   The electrocardiogram of this
patient had shown lengthening of the QT and of the PR intervals,
changes which were attributed to the myocardial lesions.

Reference has already been made to the plateau T wave in the
electrocardiogram of a child who died of vitamin D poisoning
described by Hjelt and his colleagues (1956).   There was destruc-
tion and fibrosis of myocardial muscle fibres, calcification around all
myocardial/

myocardial vessels, and many of these were thrombosed.

The cause of heart lesions in vitamin D poisoning

Ross and Williams (1939) after a study of the literature concluded that the occurrence of metastatic calcification seemed to depend more on fluctuations of serum calcium concentration than on the absolute serum level. Taking into account this view, it seems possible that the incidence of heart lesions might be more readily related to the diffusible fraction than to the serum total calcium, by analogy with the relative significance of these values in determining the onset of poisoning in the course of calciferol (vitamin D_2) treatment (Anning et al. 1948). It appears however that vitamin D can cause fibrosis and calcification of the myocardium even in the absence of hypercalcaemia, according to Andersen and Schlesinger (1942) who found such lesions in two infants who were treated with vitamin D because of persistent hypocalcaemia due to secondary hyperparathyroidism.

Hypercholesterolaemia merits consideration as a possible link between hypervitaminosis D, idiopathic hypercalcaemia and the production of vascular and myocardial lesions. A raised serum cholesterol is a feature of idiopathic hypercalcaemia of infancy (Forfar et al. 1956) as it was of vitamin D poisoning in the patient examined by me. It also appears to be associated in some way with the incidence of myocardial infarction (Lancet 1957). It seems possible therefore that/

that hypercholesterolaemia _per se_, or some form of calcium-cholesterol complex might be concerned in the production of the heart lesions of hypervitaminosis D and the lesions now being postulated in idiopathic hypercalcaemia of infancy.

Cardiac lesions in idiopathic hypercalcaemia

The post-mortem findings in a severe case of idiopathic hypercalcaemia were given by Fletcher (1957). The electrocardiogram had shown lengthening of the QT interval, but the character of the T wave was not described. Diffuse mucoid oedema of the myocardium was discovered.

Only one patient in this present series has died (Case No. 20). This child had osteogenesis imperfecta, and death occurred at the age of 14 months after an apparent recovery from idiopathic hypercalcaemia 5 months previously. The last electrocardiogram obtained at that time was normal although a previous record had shown a distinctly abnormal ST-T contour. Several sections of a routine block of tissue taken from the posterior myocardium in the region of the interventricular septum have been obtained for study, but I have been unable to find in these any lesion of the myocardium or of coronary arteries.

In those patients who initially had electrocardiographic changes and whose disease was followed to clinical recovery, the electrocardiogram returned to normal. It is nevertheless not certain that this can be taken to imply complete resolution of a heart lesion if such had indeed been present.

CONCLUSIONS

The conclusions to be drawn from this investigation of the electrocardiographic features of idiopathic hypercalcaemia may be summarized as follows:

1. The raised serum calcium of idiopathic hypercalcaemia causes shortening of the ST segment and this is characteristic of other types of hypercalcaemia, such as that induced by the intravenous injection of calcium gluconate.

2. Shortening of the corrected QT interval (QTc) reflects shortening of the ST segment in other types of hypercalcaemia but not in idiopathic hypercalcaemia. Therefore in this disease the length of the corrected QT interval (QTc) is valueless as an index of the degree of hypercalcaemia.

3. The QT interval (QTc) in idiopathic hypercalcaemia is prevented from shortening by a prolonged T wave.

4. The contour of the ST-T complex in idiopathic hypercalcaemia is often abnormal. The T wave is prominent and its apex is flattened.

5. This change in contour of the ST-T complex is not directly related to the level of serum calcium but bears a close resemblance to that found in some cases of vitamin D poisoning.

6. The absolute intake of vitamin D in idiopathic hypercalcaemia is unlikely/

unlikely to be the critical factor in producing this specific electrocardiographic change.

7. It is possible that the electrocardiographic changes in idiopathic hypercalcaemia may reflect an organic lesion of the heart caused by vitamin D, and this possibility is to be considered in Part III of these investigations.

Author's Investigations

PART   III

VITAMIN D AND HEART LESIONS IN THE RABBIT

Page

ELECTROCARDIOGRAPHY IN IDIOPATHIC HYPERCALCAEMIA AND OTHER CATION DISORDERS OF CHILDHOOD

PART III

VITAMIN D AND HEART LESIONS IN THE RABBIT

PREAMBLE

Electrocardiographic signs of idiopathic hypercalcaemia of infancy have been found to resemble those of vitamin D poisoning, and the possibility has been raised that they might reflect lesions of the coronary arteries or of the myocardium caused by vitamin D. If such were the case it would be important to know not only the site but also the natural history of the lesions so produced. Importance is attached to this problem because of the widespread use of vitamin D in infancy and because some patients with pronounced electrocardiographic signs had apparently been given amounts of vitamin D no greater/

greater than those received by many healthy infants in the community. The literature of idiopathic hypercalcaemia provides no solution to the problem because of the low mortality rate of the disease and therefore a dearth of detailed references to the histology of the heart.

It was decided to study the effect of vitamin D on the heart of the rabbit, and three problems were in mind when this experiment was undertaken:

1. The intake of vitamin D necessary to produce heart lesions.

2. The site of lesions caused by vitamin D, and their behaviour after the cessation of its administration.

3. The toxicity of vitamin D_3 compared with that of synthetic vitamin D_2 which is added to preparations of cod-liver oil, milk and cereals designed for infants.

The young rabbit was chosen for the experiment because it had been established that heart lesions could be caused in this animal with vitamin D (Agduhr and Stenström 1930c). It is evident however that the differences between the species are such that any conclusions reached must be applied with caution to the pathology of the infant. The rabbit is herbivorous, its rate of growth cannot be related to that of the child, and its reported resistance to rickets (Pirie and Wood/

Wood 1946) might suggest a particularly high degree of sensitivity to vitamin D.

MATERIAL AND METHODS

It was planned to give to the first litter of young rabbits doses of vitamin D_3 large enough to produce damage to the heart, and to subsequent litters smaller doses of vitamin D_3 or vitamin D_2. The rabbits of each litter were to be killed at intervals after the administration of vitamin D but at least one member of each litter was to be allowed to survive until it reached maturity. The plan did not altogether succeed because litters were small, and some rabbits died or became ill and had to be killed earlier than intended.

No attempt was made to give long courses of vitamin D comparable with those used in the prophylactic treatment of infants because it was thought impossible to determine the equivalent rate of growth of the rabbit and therefore the equivalent rate of administration of the vitamin.

The experiment was carried out between February and December, 1959. Twenty-seven rabbits were studied of which 9 were controls. They belonged to 6 litters of 5 healthy does and 1 healthy buck of mixed stock. The litters were numbered 1 to 6, and each rabbit is referred to by the number of its litter followed by an alphabetical letter/

letter.

D i e t

Weaning took place at the end of six weeks and thereafter a standard diet ("Diet 18") was given to treated and control rabbits. The composition of this diet, to which vitamin D had not been added, is given in Appendix X. Fresh water and a daily allotment of greens were supplied.

Preparations and administration of vitamin D

The preparation of vitamin D_3 (Glaxo) contained one million international units per millilitre in arachis oil, and that of vitamin D_2 (Roussel), 400,000 international units per millilitre in arachis oil ("Sterogyl-15 Oral"). The same batches of vitamin D_3 and of vitamin D_2 were used throughout the experiment. A tuberculin syringe was used with a needle of the intracranial (mouse) pattern which delivered 100 drops to one millilitre of each preparation. The dose was given as a calculated number of drops, and these were allowed to fall into the mouth as it was held open by means of dissecting forceps, while the head and body were firmly held by an assistant.

Termination of experiment and post-mortem examination

A specimen of blood for the estimation of serum calcium was taken from an ear vein of 15 rabbits (11 treated, 4 controls) immediately before they were killed.

Rabbits/

Rabbits were killed by fracture-dislocation of the cervical spine, and the post-mortem examination was conducted immediately afterwards. Rabbits which died were stored in a refrigerator and the post-mortem examination in these instances was carried out within twelve hours.

At post-mortem examination the body was weighed and inspected. A naked-eye examination was made of the thoracic and abdominal viscera. Cross-sectional blocks of tissue for histology were taken from the heart, one close to the origin of the great arteries, one immediately below the atrio-ventricular valves and, in the largest hearts, one between this site and the apex. Three blocks were taken from the aorta; cross-sectional and longitudinal blocks from the descending thoracic aorta and a cross-sectional block from the upper abdominal aorta.

Specimens for histological examination were fixed in a 10% solution of formol-saline. Where necessary, tissue was decalcified before being trimmed and embedded in paraffin wax. Sections, approximately 5 microns thick, were cut from the blocks of heart and aorta. These were stained with haematoxylin and eosin, with Verhoeff's stain for elastic tissue counterstained with van Gieson's stain for collagen (Verhoeff-van Gieson), by the phosphotungstic acid haematoxylin method (P.T.A.H.) and by Kossa's method for calcium. The blocks from the controls were cut again at deeper levels and further/

further sections were stained by the haematoxylin and eosin,

Verhoeff-van Gieson and P.T.A.H. methods.

<u>Dosage of vitamin D and the course of the experiment</u>

<u>Litter 1.</u>

Four rabbits of this litter were given vitamin D_3 and the fifth

was a control.   Each treated rabbit was given 200,000 international

units of vitamin D_3 in 10 daily doses of 20,000 units from the age of

4 weeks.

One rabbit (1A) lost weight and died on the tenth day of the

experiment.   The second (1B) lost weight and died 4 days later.

The third rabbit (1C) was killed 8 weeks and the fourth (1D) 40 weeks

after the beginning of the experiment.   The control (1E) was killed

on the same day as the last treated rabbit (1D).   Further data is

given in Table XX.

<u>TABLE XX : Litter 1</u>

Rabbit No.	At beginning of experiment		Dose of vitamin D per G of body wt. (Internat. units)	At end of Experiment	
	Age(Wks)	Wt.(G)		Age(Wks)	Wt.(G)
1A	4	260	769 D_3	5.5	190
1B	"	334	599 D_3	6	246
1C	".	392	510 D_3	12	1096
1D	"	337	593 D_3	44	2504
1E	"	274	-	44	2597

Litter 2/

Litter 2.

The three rabbits of this litter were also given vitamin D_3, but the dosage of the vitamin per gram of body weight was less than that given to the rabbits of litter 1. Each was given 100,000 international units in 10 daily doses of 10,000 units from the age of 3 weeks. The first rabbit (2A) was killed 3 weeks, the second (2B) 10 weeks and the last (2C) 40 weeks after the beginning of the experiment. Further data is given in Table XXI.

TABLE XXI : Litter 2

Rabbit No.	At beginning of experiment		Dose of vitamin D per G of body wt.	At end of experiment	
	Age(Wks)	Wt.(G)	(Internat. units)	Age(Wks)	Wt.(G)
2A	3	272	368 D_3	6	809
2B	"	350	286 D_3	13	2076
2C	"	374	267 D_3	43	3282

Litter 3.

Three rabbits (A, B, C) of a litter of seven weighing 35, 37 and 42 grams were killed by their mother on the day of birth. This mother subsequently gave birth to litter 5.

Litter 4.

Four rabbits of this litter were given vitamin D and the fifth was a control. Each treated rabbit was given 200,000 international units of vitamin D_2 in 10 daily doses of 20,000 units from the age of 5 weeks.

One/

One rabbit (4A) lost weight and died 3 weeks after the beginning of the experiment and the second (4B) 5 weeks later. The third (4C) was killed 13 weeks and the fourth treated rabbit (4D) together with the control (4E) 35 weeks after the beginning of the experiment. Table XXII gives details of this litter.

TABLE XXII : Litter 4

Rabbit No.	At beginning of experiment		Dose of vitamin D per G of body wt.	At end of experiment	
	Age(Wks)	Wt.(G)	(Internat. units)	Age(Wks)	Wt.(G)
4A	5	870	230 D_2	8	532
4B	"	577	347 D_2	13	906
4C	"	604	331 D_2	18	2240
4D	"	472	423 D_2	40	1950
4E	"	539	---	40	2550

Litter 5.

Four rabbits of this litter were given vitamin D and four were controls. Two controls (5A, B) were killed at the beginning of the experiment at the age of 5 days. Two rabbits (5C, E) were then given one dose of 10,000 international units of vitamin D_3 and two others (5F, G) one dose of 12,000 international units of vitamin D_2. The doses of vitamin D_3 and of vitamin D_2 per gram of body weight were smaller than those used in earlier litters.

One rabbit which had been given vitamin D_3 (5C) and a control (5D) were killed 7 weeks after the beginning of the experiment. The other rabbit which had been given vitamin D_3 (5E) died after a short illness 16 weeks after the beginning of the experiment. The rabbits/

rabbits which had been given vitamin D_2 (5F, G) and the last control (5H) were killed 32 weeks after the beginning of the experiment. Table XXIII gives information concerning this litter.

<u>TABLE XXIII : Litter 5</u>

Rabbit No.	At beginning of experiment		Dose of vitamin D per G of body wt.	At end of experiment	
	Age(Wks)	Wt.(G)		Age(Wks)	Wt.(G)
5A	5/7	45	–	5/7	45
5B	"	39	–	5/7	39
5C	"	81	123 D_3	8	1376
5D	"	68	–	8	1258
5E	"	97	103 D_3	17	1660
5F	"	93	129 D_2	33	2908
5G	"	78	154 D_2	33	2190
5H	"	103	–	33	2725

<u>Litter 6.</u>

Each of the three rabbits in this litter was given 12,000 international units of vitamin D_2 in three daily doses of 4,000 units at the age of three weeks.   The dose of vitamin D_2 per gram of body weight was approximately one-third of that given in litter 5.   One rabbit (6A) was killed 4 weeks after the beginning of the experiment. The next was killed 6 weeks after the beginning of the experiment (6B) because it began to lose weight and became seriously ill.   The last (6C) died 10 weeks after the beginning of the experiment.   Table XXIV gives further details of this litter.

<u>TABLE XXIV/</u>

TABLE XXIV : Litter 6

Rabbit No.	At beginning of experiment		Dose of vitamin D per G of body wt.	At end of experiment	
	Age(Wks)	Wt.(G)	(Internat. units)	Age(Wks)	Wt.(G)
6A	3	315	38 D_2	7	1170
6B	3	318	38 D_2	9	683
6C	3	326	37 D_2	13	848

RESULTS

Heart lesions

The naked-eye examination of two rabbits (4B, 5E) revealed that they had died in congestive heart failure; there were effusions into the pleural and peritoneal cavities, the liver was large and congested, and the heart was dilated. The hearts of these and of other rabbits which had received vitamin D seemed unduly heavy when compared with their body weight and the heart and body weight of controls (Table XXV). In 6 instances (2B; 4B, D; 5E; 6B, C) the heart weight exceeded 0.4% of the body weight the upper limit given by Schauder (1922) for the healthy rabbit.

Histology revealed lesions of the myocardium in 6, of coronary arteries in 1 and lesions subjacent to the endocardium in 10 rabbits which/

which had been given vitamin D.   The distribution of heart

lesions is given in Table XXV.

A more extensive search was made of the material from the control

animals but in none of them was any heart lesion detected.

TABLE XXV.   Heart lesions in rabbits treated with vitamin D.
             Body and heart weights at death of treated rabbits
             and of 4 controls.
             + = present, − = absent.
             * = myocardial hypertrophy in rabbits dying
                  in congestive heart failure.

Rabbit No.	Wt. at death (G)		Heart Lesions		
	Body	Heart	Myocardium	Coronary Arteries	Subendocardium
1A	190	−	+	−	+
1B	246	−	+	−	+
1C	1096	−	−	−	+
1D	2504	9	−	−	−
1E	2597	5	C O N T R O L		
2A	809	−	−	−	−
2B	2076	10	−	−	+
2C	3282	8	−	−	−
4A	532	−	+	−	+
4B	906	11	*+	−	+
4C	2240	8.5	−	−	−
4D	1950	9	−	−	+
4E	2550	6	C O N T R O L		
5C	1376	4	−	−	−
5D	1258	3	C O N T R O L		
5E	1660	22	*+	−	+
5F	2908	7	−	−	+
5G	2190	7	−	−	−
5H	2725	5	C O N T R O L		
6A	1170	4	−	−	+
6B	683	4.5	−	+	−
6C	848	4.5	+	−	−

Myocardium/

A.
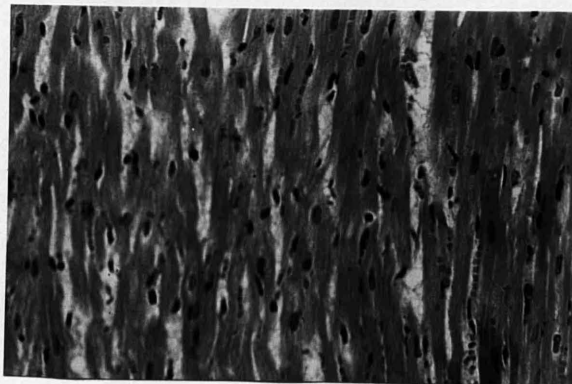
B.

Fig. 15. <u>Myocardium of left ventricle</u>.   H&E.   x 190.

A.   Normal muscle fibres of control rabbit (4E).

B.   Hypertrophy of muscle fibres in treated
     rabbit dying in congestive heart failure (5E).
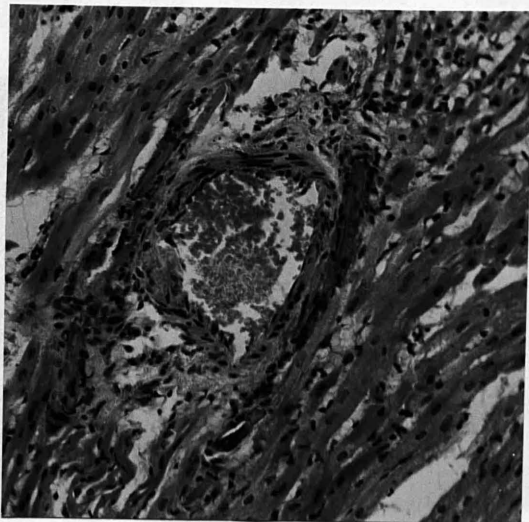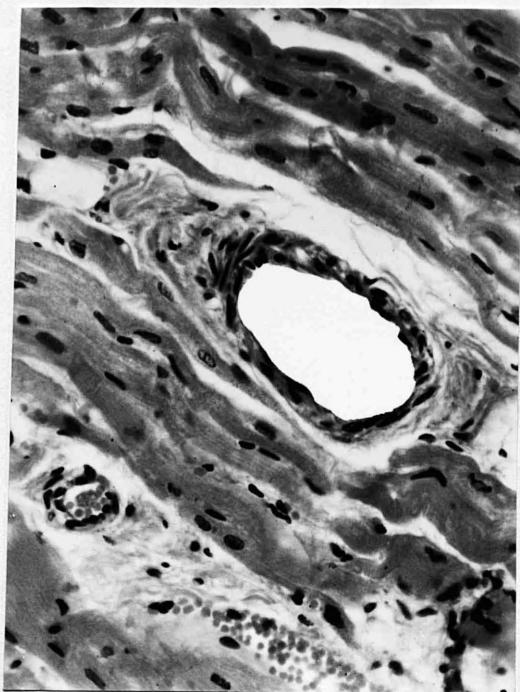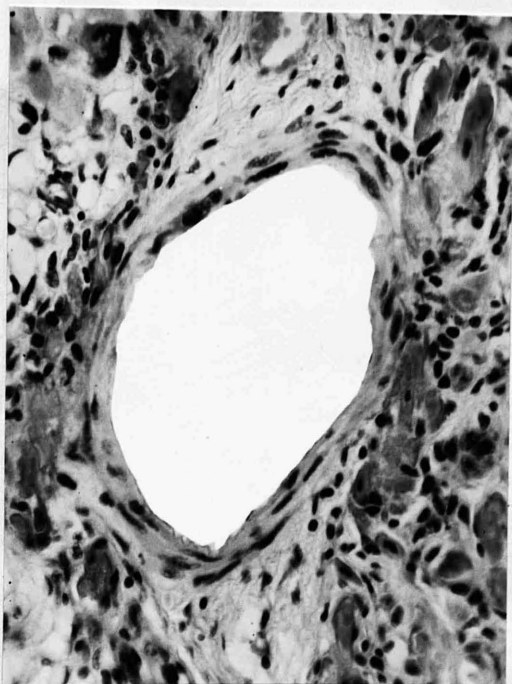
Fig. 16. Peri-arterial lesion of left ventricular myocardium.

A. Treated rabbit 1B. H&E. x 190. Calcified
    muscle cells on two sides of a small coronary artery.

B. Control rabbit 4E. H&E. x 350. Normal
    myocardium surrounding small coronary artery.

C. Treated rabbit 4A. H&E. x 350. Darkly stained
    muscle cells containing calcium around small
    coronary artery. Macrophage and giant cell
    reaction.

A.

B.
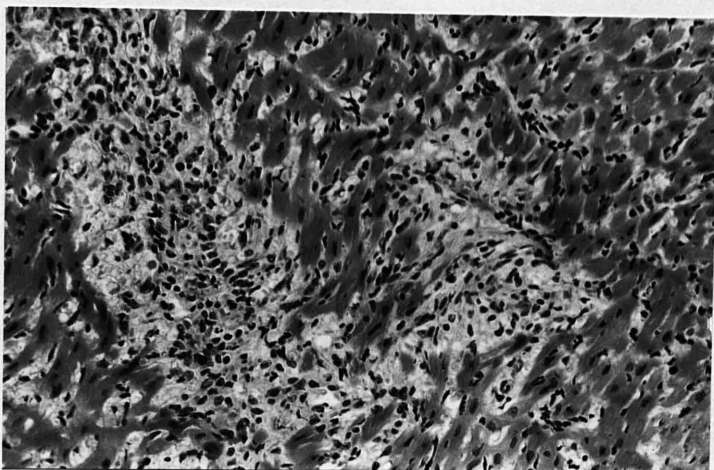
Fig. 17. <u>Pararterial lesion of left ventricular myocardium.</u>
Rabbit 6C.

A. P.T.A.H. x 40. Darkly stained normal myocardium
surrounding the lesions which appear as pale areas
unrelated to coronary arteries. The pale staining
material around the three coronary arteries is
normal adventitia.

B. H&E. x 190. At a higher magnification the lesion
is seen to consist of granulation tissue containing
macrophages and eosinophils and is surrounded by
normal muscle cells.
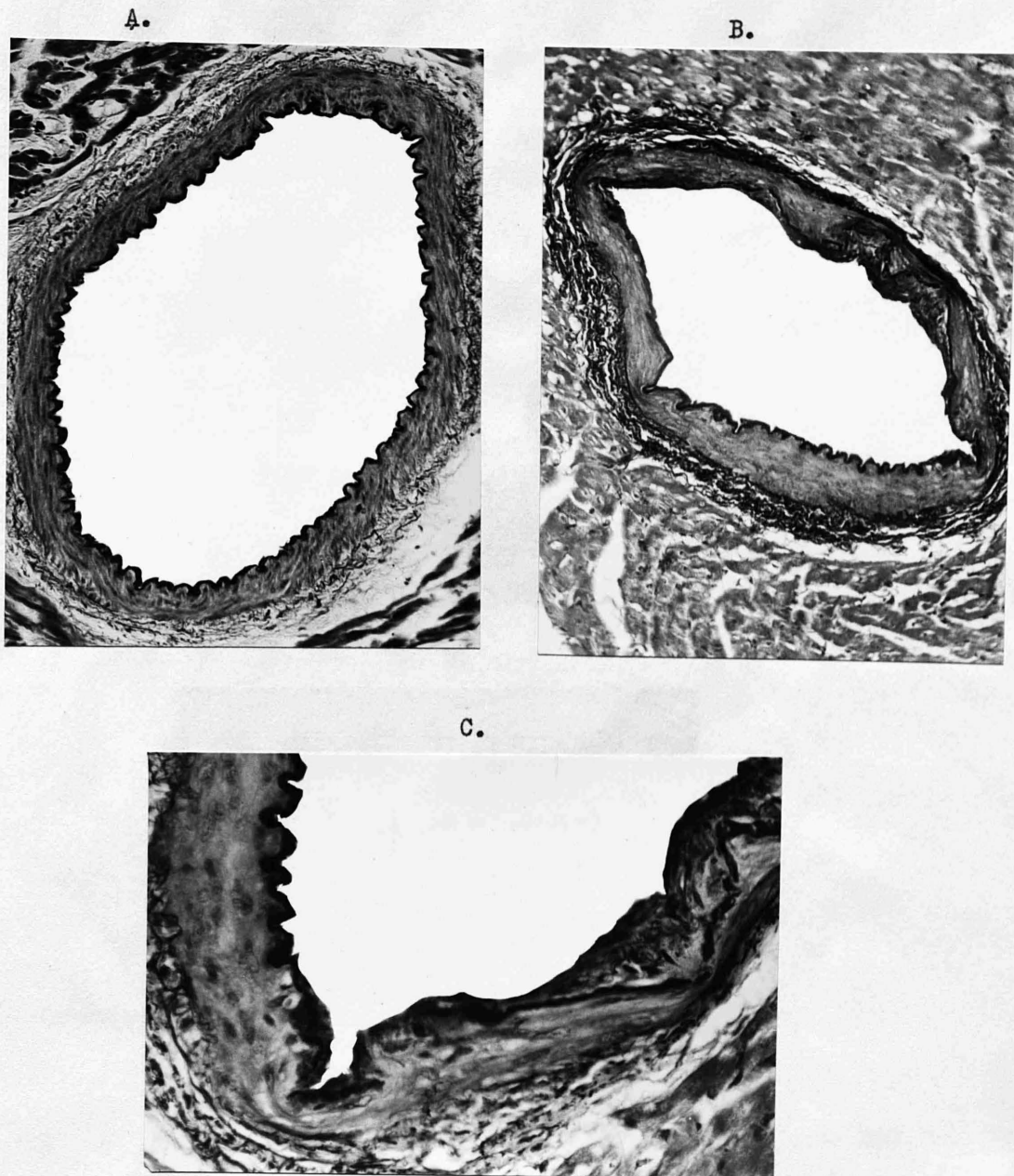
Fig. 18. <u>Coronary artery lesion.</u> Verhoeff-van Gieson.

    A.   x 150.   Normal left ventricular vessel of control rabbit (5H).

    B.   x 150.   Left ventricular vessel of treated rabbit (6B). The lower third of the wall is probably normal. The remainder of the wall shows distortion and thickening of the internal elastic lamina, and distortion of the media.

    C.   x 350.   Same vessel as B. The right-hand side of the wall shows intimal thickening with proliferation of elastic fibres, and distortion of the media.

A.
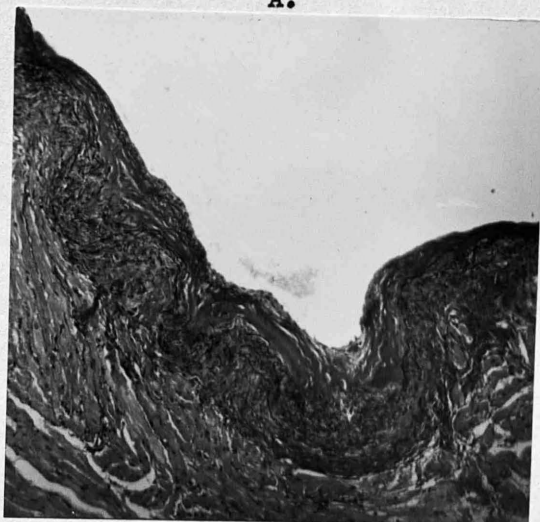
B.
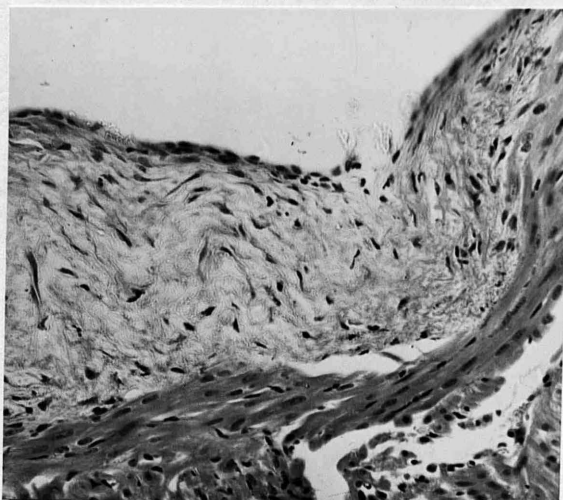
Fig. 19.   Subendocardial lesion in left atrium.

A.   Treated rabbit (1C).   Verhoeff-van Gieson.   x 85.
Proliferation of subendocardial fibrous tissue.
There is a collagenous layer immediately below the
endothelium and deep to this a fibro-elastic layer.

B.   Treated rabbit (6A).   H&E.   x 350.   Proliferation
of subendocardial fibrous tissue overlying normal
muscle.
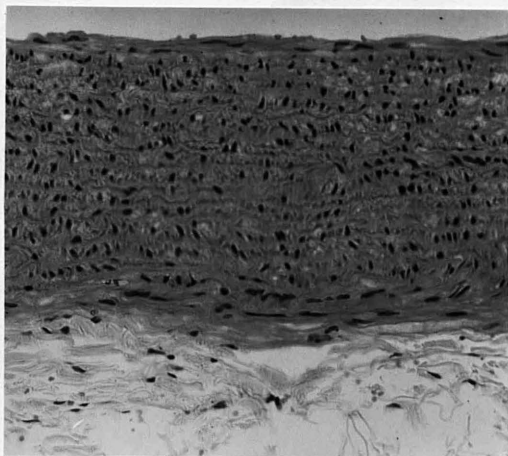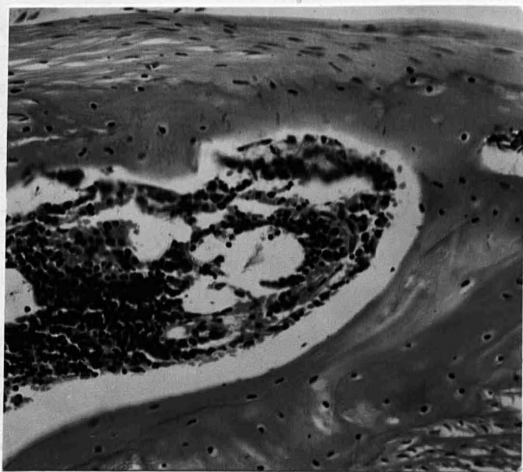
Fig. 20. <u>Descending thoracic aorta</u>. Longitudinal sections. H&E. x 190.
- A. Normal aorta of control rabbit (1E).
- B. Early aortic lesion in treated rabbit (6A). Intimal thickening. Elastic laminae are thickened, straightened and stain with haematoxylin. Centrally there is fibroblast proliferation. Adventitia and outer media are unaffected.
- C. Advanced aortic lesion in treated rabbit (5C). Intimal thickening. Disruption and thickening of elastic laminae with cartilage formation between. To the left fibroblasts and macrophages replace the normal structure.
- D. Advanced aortic lesion in treated rabbit (1D). Bone and marrow formation in the inner part of the media. Overlying intimal thickening.

Myocardium

Hypertrophy of muscle fibres but no other myocardial lesion was detected in the two rabbits (4B, 5E) which died in congestive heart failure (Fig. 15).

Focal lesions of the myocardium found in three instances (1A, 1B, 4A) were closely similar, but least extensive in rabbit 1B. These lesions were adjacent to small coronary arteries but no lesion of the arterial walls was detected (Fig. 16). Close to the vessels there were dead muscle cells, a conclusion based on the absence of nuclei and of cross-striations. The cytoplasm of some cells stained with haematoxylin and this was taken to indicate the presence of calcium; this was confirmed by a positive Kossa reaction in adjacent sections. In some places muscle cells had apparently disintegrated to form amorphous eosinophilic debris. In relation to the dead muscle fibres there was a cellular reaction. Most were macrophages and fibroblasts but there were also a few multi-nucleate giant cells.

In one rabbit (6C) there were scattered myocardial lesions which, in contrast to those just described, did not appear to be related to arteries (Fig. 17). Accordingly these lesions are described as pararterial, and the others as periarterial. There was a patchy loss of muscle fibres with replacement by granulation tissue in which were many macrophages and eosinophils and occasional giant/

giant cells.   There was no evidence of calcium deposition.

Coronary arteries

Lesions of coronary arteries were detected in only one rabbit
(6B), but in this instance there were no lesions of the muscle.
Several abnormal small coronary arteries were found in the anterior
wall of the left ventricle (Fig. 18).   The normal undulations of the
internal elastic lamina had largely disappeared and sharp angles were
formed by adjacent parts of the lamina.   This appearance gave the
impression that the normal flexibility of the elastic lamina had been
lost.   In addition to this there was thickening of the intima and
narrowing of the media.

Subendocardium

A lesion subjacent to the mural endocardium was detected in 10
rabbits (Fig. 19).   It was found in the left atrium in 8 (1A, B, C;
2B; 4A; 5E, F; 6A), in the left ventricle in 3 (1A; 4B, D) and in
the right ventricle in 2 (1A; 4B).   Immediately beneath the endo-
cardium there was a collagenous layer containing only a few fibro-
blasts.   In some instances there was a deeper layer which consisted
of fibro-elastic tissue, and this sometimes surrounded islands of
muscle cells.

A o r t a

A lesion of the aorta was found in every treated rabbit but in

none/

none of the controls.   In most of the treated rabbits the descending thoracic aorta was inelastic, its lining looked irregular and felt rough.

On microscopic examination the severity and the extent of the lesion were found to vary from rabbit to rabbit.   In 13 a lesion was found in every section examined (1A, B, C, D;   4A, B, C, D;   5C, F;   6A, B, C), but in 5 a lesion was found only in the thoracic or in the abdominal aorta (2A, B, C;   5E, G).

The inner third or half of the media was most severely affected but the related intima was often thickened (Fig. 20).   The elastic fibres were distorted and in the most severe lesions they were disrupted.   Haematoxylin staining of thickened elastic fibres was taken as evidence of calcium deposition, and this was confirmed in 10 rabbits by a positive Kossa reaction.   The least severe lesions were the most cellular, and in these there were many fibroblasts and macrophages.   Between the elastic laminae muscle cells were destroyed, and there was replacement by cartilege in the more florid lesions and by bone in one instance (1D).   The adventitia was never involved.

Serum calcium and heart lesions

The serum calcium levels of 15 rabbits (11 treated, 4 controls) immediately before they were killed are given in Table XXVI and related/

related to dosage of vitamin D, the incidence of heart lesions
and the length of time from the administration of vitamin D to
death.

TABLE XXVI. Serum calcium levels of 15 rabbits related to
other experimental data.

Rabbit No.	Vitamin D3/D2 (internat. units per G body wt. or control)		Serum Calcium (mg./100 ml.) before death	SITE OF HEART LESIONS	Days from administration of vitamin D to death
1C	D_3	510	12.2	Subendocardium	49
1D	D_3	593	13.8	NONE	270
1E	C O N T R O L		11.5	NONE	-
2A	D_3	368	19.3	NONE	14
2B	D_3	286	13.3	Subendocardium	63
2C	D_3	267	14.1	NONE	270
4C	D_2	331	9.7	NONE	84
4D	D_2	423	14.1	Subendocardium	237
4E	C O N T R O L		11	NONE	-
5C	D_3	123	11.3	NONE	49
5D	C O N T R O L		10	NONE	-
5F	D_2	129	12.9	Subendocardium	228
5H	C O N T R O L		11.1	NONE	-
6A	D_2	38	16.7	Subendocardium	25
6B	D_2	38	13.4	Coronary Arteries	39

With two exceptions (4C, 5C) the serum calcium levels of treat-
ed rabbits were substantially higher than those of the controls even
as long as 38 weeks after the cessation of treatment.   There did
not appear to be any constant association between the level of serum
calcium at death and the presence or absence of heart lesions.   Nor
was there any constant association between the amount of vitamin D
given/

given and the level of the serum calcium at death.

Incidence of heart lesions related to dosage of vitamin D

The relationship between the dose of vitamin D_3 or of vitamin D_2 and the incidence of heart lesions is given in Table XXVII. Periarterial lesions of the myocardium occurred in three rabbits (1A, 1B, 4A) of the two litters which received the largest total doses of vitamin D_3 and vitamin D_2. In relation to body weight, however, the amount of vitamin D_2 given to rabbit 4A was less than half the amount of vitamin D_3 given to rabbits 1A and 1B. Moreover there were five treated rabbits in these two litters in which no periarterial lesion was detected.

The pararterial lesions of the myocardium were found in a rabbit (6C) of the litter given the smallest doses of vitamin D_2 in relation to body weight and the only rabbit in which lesions of coronary arteries were detected (6B) belonged to the same litter.

Lesions beneath the endocardium were detected more often than other heart lesions and occurred after both the largest and smallest doses of vitamin D_3 and vitamin D_2.

Hypertrophy of the ventricular myocardium in association with congestive heart failure was found in a rabbit which had received a very large dose of vitamin D_2 (4B) and in one which had received a much smaller dose of vitamin D_3 (5E).

TABLE XXVII/

TABLE XXVII.   Dosage of vitamin D and incidence of heart lesions.

+ = present: — = absent;   * = muscle hypertrophy
only

Rabbit No.	Vitamin D3/D2 in international units per G body wt.		Total dose of vitamin D (Internat. units)	HEART LESIONS		
				Myocar-dium	Coro-nary Artery	Subendo-cardium
1A	D_3	769	200,000	+	—	+
1B	D_3	599	"	+	—	+
1C	D_3	510	"	—	—	+
1D	D_3	593	"	—	—	—
2A	D_3	368	100,000	—	—	—
2B	D_3	286	"	—	—	+
2C	D_3	267	"	—	—	—
5C	D_3	123	10,000	—	—	—
5E	D_3	103	10,000	*+	—	+
4A	D_2	230	200,000	+	—	+
4B	D_2	347	"	*+	—	+
4C	D_2	331	"	—	—	—
4D	D_2	423	"	—	—	+
5F	D_2	129	12,000	—	—	+
5G	D_2	154	12,000	—	—	—
6A	D_2	38	12,000	—	—	+
6B	D_2	38	12,000	—	+	—
6C	D_2	37	12,000	+	—	—

Incidence of heart lesions related to time of death

The relationship between the incidence of heart lesions and the time elapsing between the administration of vitamin D and death is set out in Table XXVIII.   The periarterial lesions of the myocardium were found in three rabbits (1A, 1B, 4A) which died within 10 days after the administration of vitamin D had ceased.   No other rabbit died/

TABLE XXVIII. Incidence of heart lesions in relation to length of time elapsing between the last dose of vitamin D and death.

+ = present: − = absent: * = muscle hypertrophy only.

Rabbit No.	Vitamin D3/D2	Days from administration of vitamin D to death	HEART LESIONS		
			Myocardium	Coronary Artery	Endocardium
1A	D_3	0	+	−	+
1B	"	4	+	−	+
1C	"	49	−	−	+
1D	"	270	−	−	−
2A	"	14	−	−	−
2B	"	63	−	−	+
2C	"	270	−	−	−
5C	"	49	−	−	−
5E	"	111	*+	−	+
4A	D_2	10	+	−	+
4B	"	43	*+	−	+
4C	"	84	−	−	−
4D	"	237	−	−	+
5F	"	228	−	−	+
5G	"	228	−	−	−
6A	"	25	−	−	+
6B	"	39	−	+	−
6C	"	70	+	−	−

died/

died or was killed so soon after the beginning of the experiment. The pararterial lesion of rabbit 6C was present when this animal died $9\frac{1}{2}$ weeks after the end of its course of vitamin D_2.

The coronary artery lesion of rabbit 6B was discovered when this rabbit was killed $5\frac{1}{2}$ weeks after the course of vitamin D.

Subendocardial lesions were found as early as the tenth day of the administration of vitamin D_3 (1A) and the tenth day after a course of vitamin D_2 (4A), and as late as 16 and 34 weeks respectively after the administration of vitamin D_3 (5E) and vitamin D_2 (4D) had ceased.

The rabbits with hypertrophy of the myocardium died in congestive heart failure 6 weeks (4B) and 16 weeks (5E) after the administration of vitamin D had ceased.

DISCUSSION

The significance of the aortic lesion

In six of the eighteen rabbits treated with vitamin D no lesion of the heart was detected. It is therefore important to ascertain that the preparation was active and that it was retained. For this reason attention has been paid to the aortic lesions which were found

in/

in every treated animal.

It has been known for a long time that degenerative changes and calcium deposition in the wall of the aorta may follow the administration of vitamin D to rabbits (Innes 1931, Göttche and Kellner 1932, Orzechowski and Schreiber 1934), and that the inner part of the media suffers most severely (Kreitmair and Moll 1928). A similar lesion of the aorta, but occurring spontaneously in apparently healthy rabbits, has been described by Kesten (1935) and other authors. The incidence of this lesion, referred to as "spontaneous medial degeneration" or "arteriosclerosis", appears to vary considerably from one laboratory to another, and this has been ascribed to the operation of genetic factors (Zeek 1933). In the present experiment it is considered significant that lesions of the inner media of the aorta were found with ease in every treated animal but in none of the controls even after the tissue blocks had been cut into again at deeper levels and further sections examined. It is submitted therefore that these aortic lesions were the result of vitamin D poisoning and proof of the activity and retention of the doses used.

The site and pathogenesis of lesions

Heart lesions were found only in the rabbits which had been given vitamin D, and these lesions did not accord with the description of those said to occur spontaneously in this species (Jaffé and Gavallér 1958/

1958).

Lesions immediately beneath the mural endocardium were found in 10 rabbits, focal lesions of the myocardium in 4 and lesions of coronary arteries in one.   In 3 rabbits the myocardial lesions were periarterial.   As regards susceptibility to lesions, their absolute incidence suggests that the aortic wall is more vulnerable than the subendocardial tissue, and this more vulnerable than the periarterial myocardium.   In this respect it is of interest to recall that Göttche and Kellner (1932) considered the aorta more vulnerable than the heart to the toxic action of vitamin D_2 not only in the rabbit but also in the dog, cat, rat, guinea pig and mouse.

Woerner (1959) has emphasised that the intima and inner third of the media of arteries receive their blood supply directly from that flowing through the vessel.   If the arterial endothelium is accepted as an extension of the mural endocardium it seems probable that this and the immediately subjacent tissue receive their blood supply directly from the heart chambers.   One might postulate therefore that the lesions of the aorta, of the subendocardium and of coronary arteries shared a common mode of production, and that they were the response to the diffusion of a toxic substance through the endothelium from the passing stream of blood.

The periarterial distribution of the myocardial lesions found in 3 rabbits makes it seem unlikely that they were caused by anoxia through/

through ischaemia, but more likely that they too were caused by some toxic substance. However the reason why lesions should have been so strictly confined to this periarterial distribution is not clear.

Whether the toxic substance invoked in this argument could be vitamin D or some related substance is uncertain. The correlation of incidence of heart lesions with levels of serum calcium immediately before death, gives no reason to suppose that calcium per se might have been the toxic substance concerned.

No satisfactory explanation can be afforded to account for the myocardial lesion which in one rabbit was pararterial, and consisted of a patchy replacement of muscle by granulation tissue. The distribution suggests ischaemic anoxia as the casual factor, but those coronary arteries examined were patent and their walls did not seem abnormal. It is conceivable nevertheless that blood flow had been reduced because of lesions of coronary arteries not examined. There remains at least a possibility however that the aortic lesion had encroached upon the mouth of the parent vessel or had reduced the diastolic filling pressure by causing incompetence of the aortic valve.

The two rabbits which died in congestive heart failure showed hypertrophy of the left ventricular myocardium, and in several rabbits given vitamin D the weight of the heart exceeded normal limits.

In/

In each instance there was a severe aortic lesion, and it is consider-
ed that this was at least partly responsible for myocardial hyper-
trophy.

The prognosis of lesions

The ultimate prognosis of lesions is particularly difficult to
estimate.   This is partly due to their uneven incidence but also
because of the possibility that lesions present long after the
administration of vitamin D had ceased might have resulted from the
prolonged activity of vitamin D rather than from a brief assault by
the vitamin many weeks before.   This possibility is suggested by
the persistence of high levels of serum calcium in some rabbits many
weeks after the course of vitamin D had ended.

The periarterial calcinotic lesions of the myocardium were
present as early as the tenth day of the experiment but were never
found later than the tenth day after the administration of vitamin D
had ceased.   It is arguable that lesions had been present in members
of the same litter examined later, but that they had healed.   Such
lesions might have been expected however to heal by fibrosis rather
than by complete restoration of the normal tissue architecture, but
no trace even of a healing lesion was found in two rabbits (4B, 1C)
killed 5 and 6 weeks after two others of the same litters (4A, 1B)
which had periarterial lesions.   For this reason it is suspected
that where they were not found, such lesions had never existed.

The/

The prognosis of myocardial degeneration and calcification caused in the young animal by vitamin D had been variously assessed. From studies of this problem in several species, von Brand and Holtz (1929) decided that substantial decalcification of calcinotic lesions could occur. Agduhr and Stenström (1930a) concluded that myocardial lesions never healed completely and Schmidtmann (1929) that it was not possible for them to heal. As to the uneven incidence of heart lesions observed in this experiment, Agduhr (1926) was impressed by this same feature when studying heart lesions in mice all given the same dose of vitamin D and treated under identical conditions.

The replacement of muscle by granulation tissue in the rabbit with pararterial lesions of the myocardium justifies the belief that in this animal at least, healing would have taken place by the formation of fibrous scars.

Even if these predictions as to the prognosis of such lesions are correct, it is by no means certain that any residual lesion would be extensive enough to have an appreciable effect on myocardial function especially in a growing animal. The same problems concerning the extent of repair and the effect of an incompletely healed lesion on function apply to the coronary artery lesions found in one rabbit. It would be unwise to assume that such lesions could not heal completely, yet when their state of development at the time of examination is taken into account together with the opinions expressed by Wright (1950), Duguid (1954) and Gillman (1957), it is just conceivable/

conceivable that the medial lesion, causing loss of resilience, combined with the intimal lesion might favour the deposition of thrombus and the eventual occlusion of affected vessels.

The fate of lesions subjacent to the endocardium is also uncertain. In two mature rabbits, lesions were found 32 and 34 weeks after treatment with vitamin D had ceased. This evidence favouring the persistence of lesions has however to be set against that imponderable factor, the effect of the persistent activity of vitamin D which was suggested by sustained hypercalcaemia.

The toxicity of vitamins D_3 and D_2

Both cod-liver oil (vitamin D_3) and preparations of vitamin D_2 have been shown to give rise to muscular and arterial lesions of the heart (Agduhr and Stenström 1921-31, Herlitz et al. 1929). In the present experiment, the administration of vitamin D_3 led to subendocardial lesions in 5 rabbits and to focal lesions of the myocardium in 2. The administration of vitamin D_2 led to subendocardial lesions in 5, to focal lesions of the myocardium in 2 and to coronary artery lesions in 1. However, when dosage is related to body weight it is apparent that the doses of vitamin D_3 given to litter 1 and to litter 2 in which lesions were found in 4 of 7 rabbits, were substantially greater than those given to litter 4 and to litter 6 respectively, in which lesions were found in 6 of 7 rabbits. These findings suggest that under the conditions of the experiment vitamin D_2 was more toxic than vitamin D_3. It is quite remarkable however that lesions of coronary/

coronary arteries and of the pararterial myocardium should have been found in two rabbits (6B, C) which received small doses of vitamin D_2 but not in others which had received much larger doses. Perhaps these two rabbits were peculiarly sensitive to vitamin D, and it is noteworthy that within 10 weeks of the beginning of the experiment one became ill and had to be killed and the other had died.

The results in relation to idiopathic hypercalcaemia

The doses of vitamin D used in this experiment were not only large but were given within a very short space of time. In these respects the conditions of the experiment differ from the prophylactic treatment of infants. The lowest amount of vitamin D_3 and of vitamin D_2 which produced periarterial lesions of the myocardium were, respectively, 599 and 230 international units per gram of body weight; calculated according to body weight the equivalent doses for an infant weighing 5 kilograms would be 3,000,000 and 1,150,000 units respectively. It is noteworthy however that the smaller doses of vitamin D_2 which produced pararterial lesions of the myocardium in one rabbit and coronary artery lesions in another of the same litter (37 and 38 units per gram) would on the same basis be equivalent to doses of 185,000 and 190,000 units for an infant of 5 kilograms, or to daily doses of 1300 units to an infant of average weight between the ends of the first and sixth months of life. According to Creery and Neill (1955), dosage of this order has often been equalled and sometimes exceeded in recent years.

Because/

Because of the rapid rate of administration of vitamin D in this experiment, these calculations of daily intake would be relevant to prophylactic treatment in infancy only if a mechanism existed whereby vitamin D failed to be inactivated or excreted and thus exerted a cumulative effect. Such a mechanism has been postulated in idiopathic hypercalcaemia (Fellers and Schwartz 1958, British Medical Journal 1960). Moreover in the severe form of the disease which is considered to be only a variant of the mild form (Lancet 1960), concentrations of vitamin D in the plasma have been found to equal those expected from the daily administration of 100,000 units of vitamin D_2 (Fellers and Schwartz 1958). If it is proved that patients suffering from the mild form of idiopathic hypercalcaemia also maintain such high plasma concentrations of vitamin D, then even the highest doses of vitamin D given to animals in this experiment, and the lesions produced by these, would be of inescapable relevance to the clinical disease.

The critical factor determining whether or not lesions will be caused by a given intake or concentration of vitamin D is likely to be the degree of sensitivity of the species in question. It is of course conceivable that the rabbit is particularly sensitive to vitamin D. Pirie and Wood (1946), for example, stated that rickets had never been reported in the rabbit, but Fresdorf (1947) described vitamin D deficiency in one animal and Gebauer (1958) was of the opinion/

opinion that the rabbit in common with other laboratory animals can develop rickets. It is certainly arguable that the term "sensitivity" is inaccurate, and that the apparent sensitivity of a species or of an individual of a species to vitamin D is merely the expression of a relatively slow inactivation or excretion of the vitamin on the part of that individual or species.

There are therefore reasons for believing that the results of this experiment may be applicable to the infant suffering from idiopathic hypercalcaemia on the assumption that in this disease there is defective excretion or inactivation of vitamin D.

I have suggested that the coronary arteries or the myocardium of the left ventricle would be the probable site of a lesion respons-ible for the electrocardiographic changes of idiopathic hypercalcaemia. Lesions at these sites have been found in the experimental material. It seems unlikely that lesions beneath the endocardium similar to those found in this experiment could cause the electrocardiographic changes which have been described. The effect of this type of lesion upon heart function might be expected to resemble that of endocardial fibroelastosis which usually involves the left ventricle and left atrium, but the electrocardiographic signs of this disease reflect chamber hypertrophy and do not resemble those of idiopathic hypercal-caemia (Nadas 1957, Keith, Rowe and Vlad 1958). Nor is there any resemblance between the electrocardiographic features of idiopathic hypercalcaemia/

hypercalcaemia and those which are reported to follow either subendocardial infarction or injury to the endocardium (Bayley 1946, Hellerstein and Katz 1948, Levine and Ford 1950).

CONCLUSIONS AND SPECULATIONS

Lesions of the aortic wall are frequently produced in the healthy young rabbit by the administration of vitamin D, and occurred in this experiment in every rabbit so treated (18 rabbits). Lesions of the heart are found less often, and of these the most frequently encountered have been situated immediately beneath the mural endocardium (10 rabbits). Periarterial calcinotic lesions of the myocardium occurred even less frequently (3 rabbits). Pararterial lesions of the myocardium and lesions of the walls of small coronary arteries were each found once.

The ultimate prognosis of the experimentally produced heart lesions is uncertain because of the apparent persistence of the activity of vitamin D long after the cessation of its administration. Even if repair of periarterial and pararterial lesions of the myocardium and of coronary artery lesions were not to proceed to a complete/

complete restoration of the normal tissue architecture, it is by no means certain that any residual lesions would exert an appreciable effect on heart function.

Both the natural vitamin D_3 and the synthetic vitamin D_2 may cause lesions of the heart. In this respect vitamin D_2 is at least as toxic as vitamin D_3 and may be more so.

To produce periarterial lesions of the myocardium extremely large doses of vitamin D are required, which in this experiment were equivalent on the basis of body weight to a dose of 3,000,000 international units of vitamin D_3 or of 1,150,000 units of vitamin D_2 for an infant weighing 5 kilograms. Pararterial lesions of the myocardium and coronary artery lesions did however follow the administration of much smaller doses, equivalent to 185,000 and 190,000 units of vitamin D_2 for an infant weighing 5 kilograms.

In contrast to its prophylactic use in infancy, vitamin D was given to rabbits in high dosage in the course of a very short space of time. The low incidence of myocardial and coronary artery lesions even after such intensive dosage makes it seem unlikely that similar lesions would occur in the healthy infant during the course of prophylactic treatment with vitamin D. It is argued however that the same might not apply to the infant suffering from idiopathic hypercalcaemia if, as has been suggested, there/

there exists in that disease a defect in the degradation or
excretion of vitamin D which may allow the vitamin to exert a
cumulative effect.

The possibility cannot be ruled out that the electrocardio-
graphic changes in idiopathic hypercalcaemia result from a
disturbance of the electrical activity of the myocardium by some
chemical mechanism rather than by an organic lesion, but further
study of a possible connexion between idiopathic hypercalcaemia
of infancy, vitamin D and heart lesions would seem to be
justified. Probable differences in species sensitivity to
vitamin D might cast doubt upon the validity of conclusions
derived from animal experiments. Useful information might how-
ever be gained from detailed histology of the heart of the few
infants who die in the course of idiopathic hypercalcaemia.

Any substance so widely used in early life as vitamin D
which is capable of causing damage to the myocardium and its
arteries seems worthy of study in a community in which disease
of the coronary vasculature is so urgent a problem.

Author's Investigations

PART IV

ELECTROCARDIOGRAPHY IN HYPOCALCAEMIA, HYPERKALAEMIA,
HYPOKALAEMIA AND HYPERNATRAEMIA

ELECTROCARDIOGRAPHY IN IDIOPATHIC

HYPERCALCAEMIA AND OTHER CATION

DISORDERS OF CHILDHOOD

PART IV

ELECTROCARDIOGRAPHY IN

HYPOCALCAEMIA, HYPERKALAEMIA,

HYPOKALAEMIA AND HYPERNATRAEMIA

PREAMBLE

In this last investigation I return to electrocardiography to describe the signs of hypocalcaemia, hyperkalaemia and hypokalaemia, and to make an assessment of their diagnostic value. The study is based on electrocardiograms recorded from 9 patients, which have been selected to illustrate certain points relevant either to opinions/

opinions expressed by other observers or to the use of electro-cardiography as a substitute for the determination of the serum calcium or potassium.

Electrocardiograms have also been recorded from 3 infants who were suffering from hypernatraemia, and the interpretation of these will be discussed.

The technique used in the recording and analysis of electro-cardiograms is the same as that used for the examination of healthy infants and is described in Appendix I.   Time intervals in the cardiac cycle of patients aged from 2 weeks to 12 months are compared with those in the electrocardiograms of healthy infants analysed in Part I of these investigations.   Measurements from electrocardiograms of younger and older patients are compared with those given for healthy children by Ziegler (1951) or by Nadas (1957).

References are given in Appendix IX to the methods in use in this hospital for the various biochemical determinations quoted. I have taken the normal range for serum calcium in infancy as being from 10.1 to 11.5 mg. per 100 ml.   This range was established in this hospital.   I have taken the normal range for serum potassium as being from 16 to 22 mg. per 100 ml. (4.1-5.6 m.Eq./l.), and that for serum sodium as being from 307 to 330 mg. per 100 ml. (133-143 m.Eq./l.).   The ranges for serum potassium and serum sodium are those given in Nelson's Textbook of Pediatrics (1959).

HYPOCALCAEMIA

Review of literature

Hypocalcaemia was the first biochemical disorder recognised to cause changes in the electrocardiogram. White and Mudd (1929) reported that hypocalcaemia was accompanied by lengthening of the QT interval. It was later shown by Aschenbrenner and Bamberger (1935) and by Marzahn (1935) that in infantile and parathyroprival tetany this was due to lengthening of the ST segment. Lengthening of the ST segment has now been accepted as the outstanding electro-cardiographic sign of hypocalcaemia and as evidence of a deficiency of ionized calcium (Yu 1952, Joos, Yu and Miller 1954, Schulman and Ratner 1955). The signs of hypocalcaemia (lengthening of the ST segment and QT interval) appear therefore to be the direct oppo-site of those regarded as characteristic of hypercalcaemia (shortening of the ST segment and QT interval).

Earlier studies had been made by Morgenstern in 1914 and by Schiff in 1923. Morgenstern reported that in infantile tetany the T waves were particularly tall. Schiff's study of the electrocardiogram of the "spasmophilic heart" (das Spasmophilieherz) was stimulated by a high incidence of sudden death among rachitic infants with tetany. Like Morgenstern he found strikingly tall T waves following relatively low R waves, and he considered these to be signs of tetany of the heart (Herztetanie). Neither author referred/

referred to the length of the QT interval, but the ST segments in their published electrocardiograms appear disproportionately long. As to the height of the T wave, Marzahn (1935) came to quite the opposite conclusion. He found that in parathyroprival tetany it was flattened or inverted and that it tended to resume a normal appearance after the administration of dihydrotachysterol (A.T.10). Behrendt (1949) subsequently added his support to the opinion of Morgenstern and Schiff by stating that the T wave in tetany was high and sharply peaked.

The explanation for this divergence of opinion regarding the height of the T wave may lie with the serum potassium concentration. Kramer, Tisdall and Howland (1921) reported that in infantile tetany the serum potassium was often elevated. Hypocalcaemia has been shown to potentiate the effect of hyperkalaemia on the electrocardiogram (Levine et al. 1952), and it is therefore conceivable that even mild hyperkalaemia, if associated with severe hypocalcaemia, might be sufficient to produce tall T waves similar to those described in association with potassium intoxication (page 191). Support is lent to this argument by two observations made of the effect of depletion of ionized calcium in newborn infants during replacement transfusion with citrated blood. Furman, Hellerstein and Startzman (1951) reported that the T waves became depressed during this procedure, but returned to normal after calcium gluconate/

gluconate had been given.   On the other hand, Joos, Yu and Miller (1954) reported that the T waves increased in height in two instances in which hyperkalaemia as well as hypocalcaemia was induced during the transfusion.

Clinical material

At no time during the course of this investigation was any patient suffering from infantile tetany available for examination. An account will be given of the findings in 3 patients suffering from neonatal tetany.   The third patient differed from the others in that he continued to have seizures even after the serum calcium had been raised to a normal level.

Clinical, biochemical and electrocardiographic
findings

Patient 1

J.G. was admitted to hospital at the age of 8 days.   He was slow to cry at birth, but during the first 5 days of life he was otherwise healthy.   He fed on half-cream National Dried Milk from the second day of life.   During the sixth day intermittent twitching of the face and limbs was noticed, and this continued until admission.   He then had hypocalcaemia (serum calcium 6.7 mg./100 ml.) and hyperphosphataemia (serum phosphorus 11.25 mg./100 ml.).   The serum potassium was raised (23 mg./100 ml. : 5.9 m.Eq./l.).   In the electrocardiogram (Fig. 21) there was a long ST segment (0.12 second) and a rather long QT interval (QTc 0.43).   These exceeded the maximum values recorded in healthy infants aged from 2 weeks to

3/

JG   1   2

I

II

III
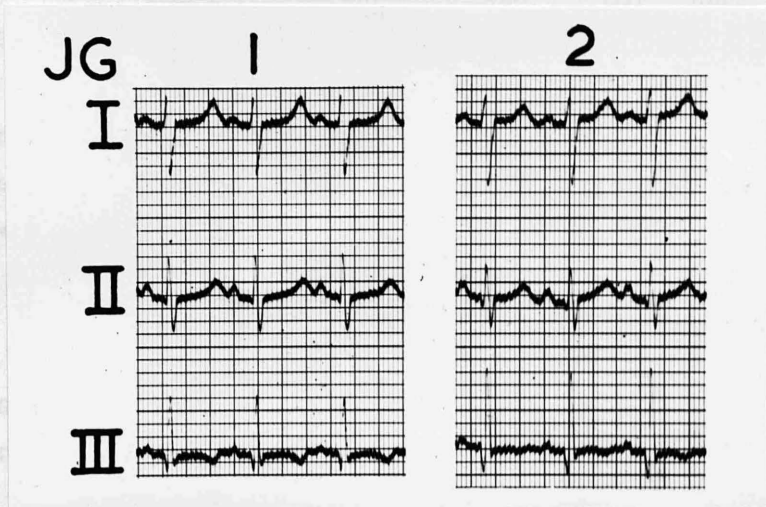
Fig. 21. <u>Hypocalcaemia in neonatal tetany</u>: Patient J.G.

    Record 1.   Age 8 days.   Serum calcium 6.7 mg./100 ml.
                  Long ST segment.   QTc 0.43.

    Record 2.   Age 10 days.   Serum calcium 12.2 mg./
                  100 ml.   ST segment shorter.   QTc 0.40.

IM   1   2

I

II

III
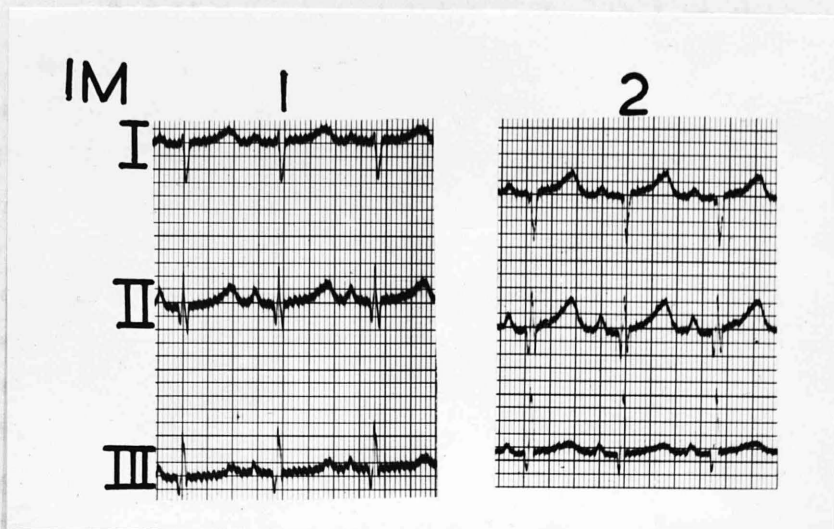
Fig. 22. <u>Hypocalcaemia in neonatal tetany</u>: Patient I.M.

    Record 1.   Age 6 days.   Serum calcium 8 mg./100 ml.
                  Long ST segment.   QTc 0.42.

    Record 2.   Age 9 days.   Serum calcium 9.6 mg./100 ml.
                  ST segment shorter.   QTc 0.395.

3 months (Part I). The ST segment was also much longer than the maximum for the first to the fourth weeks of life (0.05 second) derived from Ziegler's figures (1951), but the QTc value did not exceed his maximum for that age period (0.434). The contour of the T wave was regarded as being within normal limits.

In the course of 48 hours he was given 8 grams of calcium chloride. Twitching ceased and did not recur. The serum calcium increased to 12.2 mg. per 100 ml., and the serum phosphorus fell to 5.75 mg. per 100 ml. The serum potassium had risen further to 24 mg. per 100 ml. (6.2 m.Eq./l.). Both the ST segment (0.06 second) and the QT interval (QTc 0.40) had become shorter, and the QTc value was now unquestionably within normal limits. The appearance of the T wave was unchanged.

Patient 2

I.M. born at full-term was admitted to hospital at the age of 6 days. She had been fed on full-cream Ostermilk. She had seemed healthy, at birth and during the first 5 days of life. On the following day however muscle twitching was observed on several occasions, but there was no impairment of consciousness. At admission she was found to have hypocalcaemia (serum calcium 8 mg./ 100 ml.) and hyperphosphataemia (serum phosphorus 10.7 mg./100 ml.). The QTc value was 0.42 and the ST segment seemed unduly long when compared with the length of the T wave. As with the previous patient this QTc value exceeded the maximum recorded in healthy infants aged from 2 weeks to 3 months (Part I), but not the maximum (0.476) given by Ziegler (1951). The contour of the T wave was within normal limits (Fig. 22).

After/

After 10.6 grams of calcium chloride had been given in the course of 80 hours the serum calcium had risen to 9.6 mg. per 100 ml. and the serum phosphorus had fallen to 7.9 mg. per 100 ml. The second electrocardiogram was obtained at this time and in this the QTc value (0.395) was now unquestionably within normal limits, and the length of the ST segment had also decreased.

The length of the ST segment in the first electrocardiogram was 0.10 second, and in the second 0.07 second.   It seems permissible to compare the length of the segment in these electrocardiograms because the heart rate (which was shown in Part I to affect its length) was practically the same in both (158 and 162 per minute). The ST segment in the first electrocardiogram was longer than the maximum value derived from Ziegler's figures (0.08), but in the second it had fallen to within his normal range.

Patient 3

J.W. born at full-term was admitted to hospital at the age of 3 days.   Delivery had been uneventful and at birth he seemed healthy.   At the age of 12 hours he began to have attacks of cyanosis.   When he was 2 days old, twitching of the limbs began and continued intermittently until admission.   At admission there was hypocalcaemia (serum calcium 8.3 mg./100 ml.) and hyperphosphata-aemia (serum phosphorus 8.25 mg./100 ml.).   The electrocardiogram (Fig. 23) showed a depressed T wave and a rather long QT interval (QTc 0.425), but it was impossible to be sure whether the latter was due to a long ST segment or to a broad T wave.   The QTc value exceeded the maximum value encountered in healthy infants aged from 2 weeks to 3 months (Part I), but not Ziegler's (1951) maximum value for the first week of life (0.476).

One/
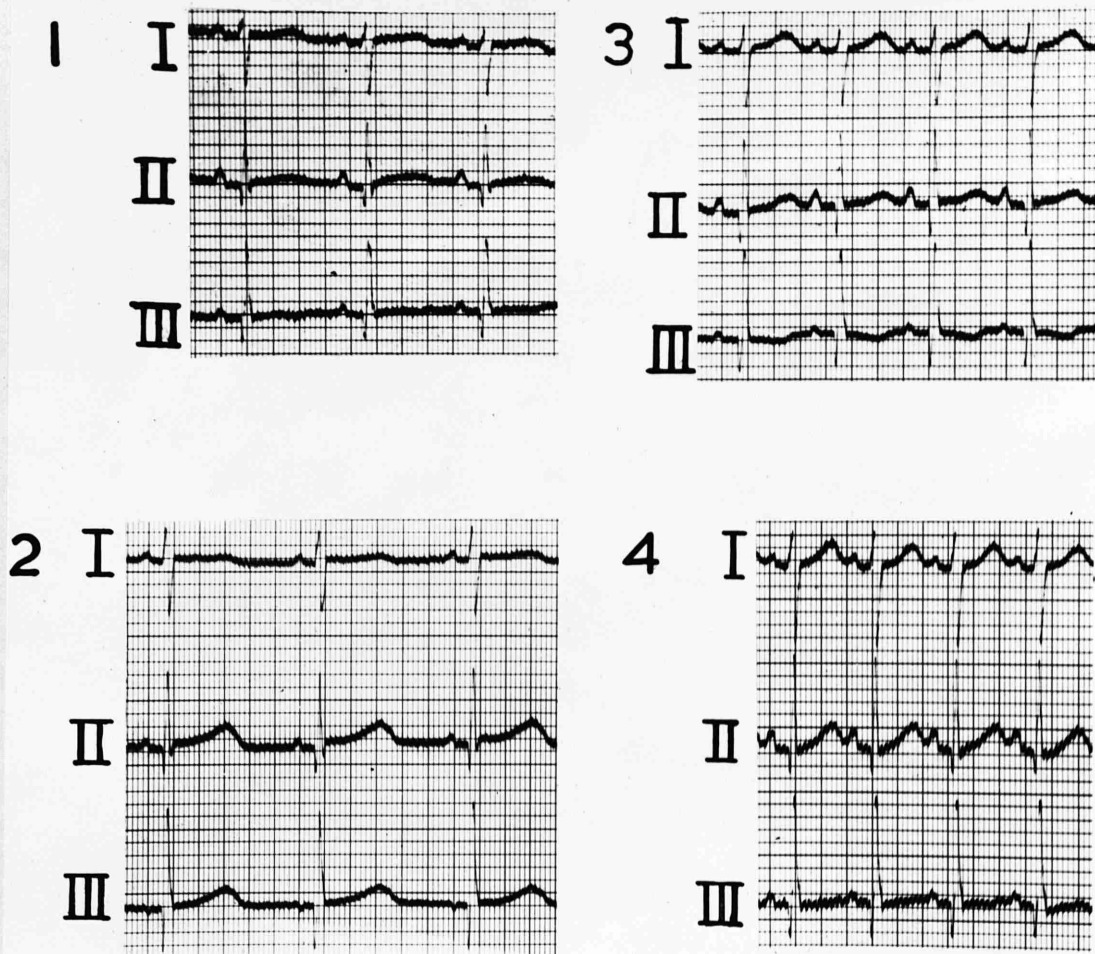
Fig. 23. Hypocalcaemia in the neonatal period: Patient J.W.

Record 1.   Age 3 days.   Serum calcium 8.3 mg./100 ml.
Depressed T wave.   QTc 0.425.

Record 2.   Age 4 days.   Two hours after 0.6G
CaCl$_2$.   Serum calcium 10.6 mg./100 ml.
Increased height of T in leads II and
III but depressed in lead I.   QTc 0.395.

Record 3.   Age 9 days.   Serum calcium 9.4 mg./100 ml.
Improved contour of T in lead I.   QTc 0.41.

Record 4.   Age 15 days.   Serum calcium 9.5 mg./100 ml.
E.C.G. within normal limits.   QTc 0.395.

One gram of calcium gluconate was given intravenously but twitching recurred after 12 hours. Next day 0.6 gram of calcium chloride was given by mouth. Two hours later the serum calcium was within normal limits (10.6 mg./100 ml.) but hyperphosphataemia persisted (7.75 mg./100 ml.). The serum potassium was slightly raised (23.3 mg./100 ml. : 5.9 m.Eq./l.). The electrocardiogram showed an increase in height of the T wave in leads II and III, and a substantial decrease in the length of the QT interval (QTc 0.395). Twitching recurred intermittently during the following 10 days, and for this reason 4 grams of calcium chloride were given daily. At the age of 9 days and again at 15 days, the serum calcium was somewhat low (9.4 and 9.5 mg./100 ml.), and hyper-phosphataemia persisted (7.5 and 7.25 mg./100 ml.), but on each occasion the electrocardiogram was considered to be within normal limits.

D i s c u s s i o n

In each patient the corrected QT interval (QTc) became shorter after the administration of calcium and the consequent rise in serum calcium. In 2 patients the ST segment was prolonged in the first electrocardiogram; in 1 of these (I.M.) it returned to within normal limits and in the other (J.G.) its length halved when the serum calcium rose. It would appear that the ST segment is the component of the QT interval responsible for the changes in the QTc value. In the third patient (J.W.) it was found impossible to measure the ST segment of the first electrocardiogram with any degree of accuracy. It would seem however that when measurement is/

is possible a lengthened ST segment is a reliable sign of
hypocalcaemia.

The need exists for some simple means of distinguishing
between myoclonic seizures due to hypocalcaemia in the early
neonatal period and seizures due to other causes, without
recourse to serum calcium estimations.   There are unfortunately
at the present time at least two objections to the use of the ST
segment of the electrocardiogram as an index of hypocalcaemia.
Too few measurements have been made of the ST segment of healthy
infants in the first 10 days of life, and such measurements as have
been made have not been related to the serum level of ionized
calcium at the time.

Measurement of the QTc value can afford little assistance in
the diagnosis of hypocalcaemia in the early neonatal period
because published figures indicate a wide scatter and particularly
high upper limits for healthy infants at this age.   Values of up
to 0.476 have been reported (Ziegler 1951), and this figure is
substantially greater than the highest value (0.415) which I
encountered in healthy infants aged from 2 weeks to 3 months or
indeed at any time later in the first year of life (Part I).   The
length of the T wave seems to be at least partly responsible for such
high QTc values.   Ziegler's figures (1951) indicate that the T
wave/

wave is longer in the first week of life than later in the neonatal period, and the T waves which I measured (Part II) before replacement transfusion in 3 infants, less than 3 days old, (0.20, 0.16, 0.18 second), were longer than those encountered in healthy infants (Part I) at any time later in the first year of life (0.15 second). No explanation can be advanced to account for this particularly long T wave.

In none of the electrocardiograms taken while the serum calcium was low was there a tall pointed T wave similar to that described by Morgenstern (1914) and Schiff (1923). There were however differences in the height of the wave as for example between the first electrocardiograms of patient J.G. in which it was of average height, and of patient J.W. in which it was distinctly low. It is perhaps of some interest that the serum potassium was raised when the first electrocardiogram of J.G. was recorded.

<div align="center">

HYPERKALAEMIA

Review of literature
</div>

The appearance of tall pointed T waves was considered by Merrill and his associates (1950) to be the earliest electrocardiographic sign of hyperkalaemia. These authors reached other important conclusions. They observed that the electrocardiographic signs of hyperkalaemia appeared earlier when hyponatraemia/
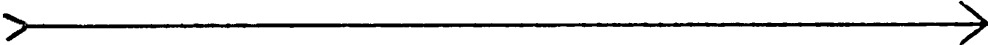
hyponatraemia was present than when the serum sodium was within normal limits. They were also of the opinion that no exact correlation existed between the clinical and electrocardiographic evidence of potassium intoxication on the one hand and the concentration of potassium in the serum on the other, and that the electrocardiogram gave more reliable information regarding the clinical status of the patient than did an estimation of the serum potassium alone. Levine and his associates (1952) confirmed that depletion of sodium enhanced the effect of hyperkalaemia on the electrocardiogram and stated that hypocalcaemia could do the same. They expressed the opinion that when hyponatraemia or hypocalcaemia accompanied hyperkalaemia the T wave might not become tall and pointed, but might be "tent-shaped" and of average height.

Other changes in the electrocardiogram caused by hyperkalaemia have been described by several authors including Winkler, Hoff and Smith (1938) and Govan and Weiseth (1946).

The sequence of electrocardiographic events reported to accompany increasing potassium intoxication are summarized in Table XXIX. The T wave becomes tall and pointed. A deep S wave follows the R wave which is small at first but later becomes taller. The sharp contour of the QRS complex is gradually lost and its component waves become broader. The ST segment is elevated/

TABLE XXIX

A diagramatic representation of electrocardiographic changes found in association with
increasing hyperkalaemia

	INCREASING HYPERKALAEMIA →			
P	Broad & flat	Atrial arrest		
PR	Prolonged			
QRS	R depressed	Tall R, Deep S	Broad & smooth	Ventricular arrhythmia and arrest
ST	Elevated	Depressed		
T	T a l l a n d p o i n t e d			
QT	Variable	Prolonged		

159

elevated at first, but is later depressed. The QT interval eventually lengthens. The P wave becomes broad and depressed and the PR interval lengthens. Atrial arrest and serious disorders of ventricular rhythm may then occur.

Clinical material

Electrocardiograms obtained from 3 patients are to be described. In 2 instances the signs were typical but in the third they were difficult to interpret. Two patients developed hyperkalaemia as a result of acute adrenocortical failure and the other as a result of acute renal failure.

Clinical, biochemical and electrocardiographic
findings

Patient 1

R.W., a girl aged 11 years, was admitted to hospital suffering from renal tuberculosis. A radiograph of chest on admission showed microcardia but although she was wasted and apathetic there was no abnormal pigmentation, hypotension or obvious dehydration. Treatment with streptomycin and isoniazid was begun but 3 days later she became desperately ill. In the space of 12 hours she vomited almost continuously, she became severely dehydrated, developed peripheral circulatory failure and lost consciousness. An electrocardiogram (Fig. 24) recorded at the same time as blood was removed for biochemical estimations showed tall pointed T waves regarded as characteristic of hyperkalaemia. The only other noteworthy/
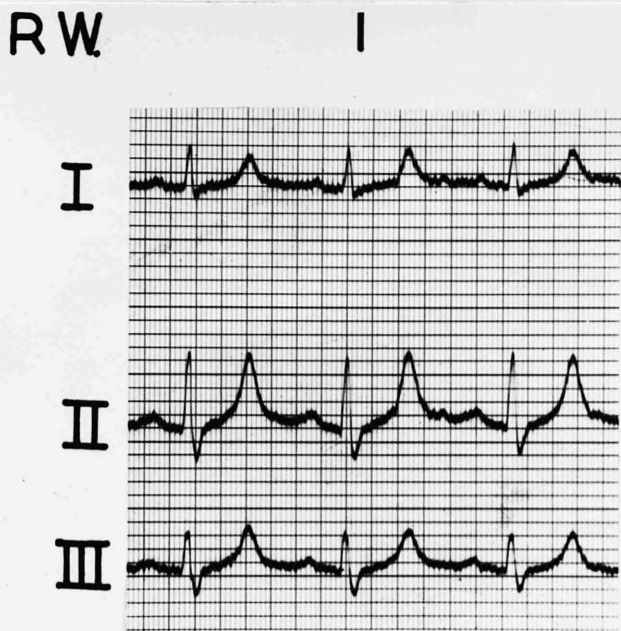
Fig. 24. Hyperkalaemia in adrenal cortical failure.

Patient R.W. aged 11 years.   Serum potassium
30 mg./100 ml. (7.7 m. Eq./l.).   Tall pointed
T waves and slightly prolonged PR interval
(PR 0.17 second).
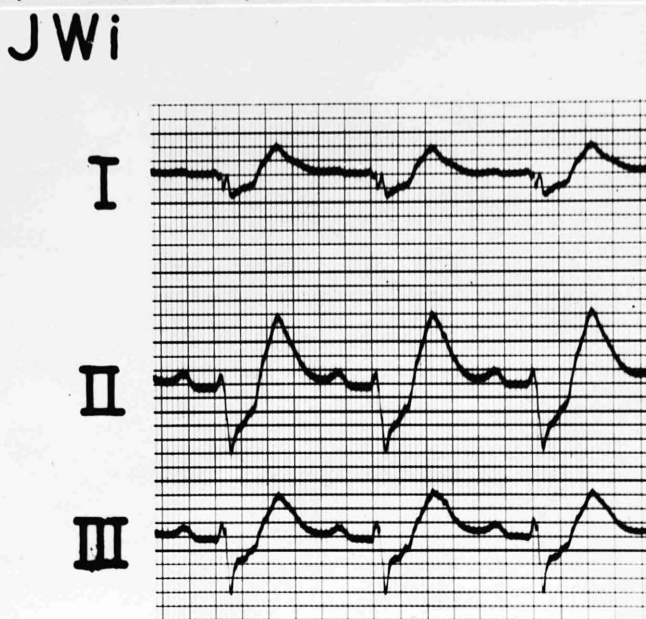
Fig. 25. Hyperkalaemia in acute renal failure.

Patient J.Wi. aged 9 days.   Serum potassium
44 mg./100 ml. (11.3 m. Eq./l.).   Tall
pointed T waves, small R waves and deep S
waves.   Prolonged PR interval (0.17 second)
and QRS complex (0.16 second).

noteworthy feature was a slightly prolonged PR interval which was 0.17 second at an average heart rate of 92 per minute as compared with 0.16 second, given by Nadas (1957) as the upper limit of normal for her age. At this time there was hyperkalaemia (serum potassium 30 mg./ 100 ml. : 7.7 m.Eq./l.), hyponatraemia (serum sodium 254.6 mg./100 ml. : 110.7 m.Eq./l.) and hypochloraemia (plasma chloride 227 mg./100 ml. : 64 m.Eq./l.). Acute adrenocortical failure was diagnosed and thought to be due to adrenal tuberculosis. Treatment with isotonic saline and 5% glucose intravenously, combined with adrenal cortical extract (Eucortone) and deoxycortone acetate (D.C.A.) produced a dramatic improvement in her clinical state. Further reference will be made to this patient during the description of the electrocardiographic features of hypokalaemia.

Patient 2

J.Wi. was admitted to hospital at the age of 9 days. He was apparently healthy at birth. For the first 7 days he throve satisfactorily but on the eighth day he began to pass loose stools and to refuse feeds. On admission he was severely dehydrated. His condition steadily deteriorated, his breathing became acidotic and he had pronounced oliguria. The urine contained red blood cells. He died 3 days after admission and at autopsy the clinical impression of renal vein thrombosis was confirmed.

The electrocardiogram (Fig. 25) 10 hours before death was typical of hyperkalaemia, with tall pointed T waves, small R waves and deep S waves. The breadth of the QRS complexes indicated complete bundle branch block. The PR interval was 0.17 second which according to Nadas (1957) is 0.06 second too long for an average heart rate of 98 per minute at this age. Biochemical analysis/

analysis revealed hyperkalaemia (serum potassium 44 mg./100 ml. :
11.3 m.Eq./l.), azotaemia (blood N.P.N. 145 mg./100 ml.), hypo-
natraemia (serum sodium 282 mg./100 ml. : 123 m.Eq./l.) but a
serum calcium within normal limits (11 mg./100 ml.).

Patient 3

N.R. was admitted to hospital at the age of $2\frac{1}{2}$ weeks, marasmic
and dehydrated.   She was a female pseudohermaphrodite with congeni-
tal adrenal hyperplasia.   A sodium-losing crisis occurred 4 days
after admission.   She became severely dehydrated and gravely ill;
the heart sounds were irregular in rate and rhythm.   There was
pronounced hyperkalaemia (serum potassium 41 mg./100 ml. : 10.5
m.Eq./l.), and hyponatraemia (serum sodium 239 mg./100 ml. : 104
m.Eq./l.).   The electrocardiogram (Fig. 26) presented a striking
picture of chaotic heart action.   She was given isotonic saline
by mouth and isotonic saline with 5% glucose intravenously.
Electrocardiograms during the following 6 hours showed a gradual
restitution of the record which reflected the clinical improvement.
The return of the electrocardiogram to a more normal pattern was
at first marked by the appearance of wide QRS complexes, but the
tall pointed T waves of potassium intoxication were not seen at
any time.

Another sodium-losing crisis occurred 2 days later.   The
levels of serum potassium and serum sodium were almost identical
with those previously encountered (serum potassium 42 mg./100 ml. :
10.8 m.Eq./l, serum sodium 241 mg./100 ml. : 104.3 m.Eq./l.).   The
electrocardiogram was however quite different on this occasion
(Fig. 27).   In leads II and III there were small R waves and deep
S waves followed by relatively large T waves.   In lead II the
summits of the T waves were sharp.   There were frequent
ventricular/

FOETAL ADRENOGENITAL SYNDROME.

IN ACUTE ADRENAL FAILURE, — BEFORE THERAPY.

E.C.G. Standard leads

I

II

III

AFTER 1 ½ HOURS OF TREATMENT.   TOTAL NORMAL SALINE - 165 ml. (1·5 gm. NaCl.)

AFTER 6 HOURS OF TREATMENT.   TOTAL NORMAL SALINE - 290 ml. (2·6 gm. NaCl.)
GLUCOSE - 7·5 gm. Intravenously.
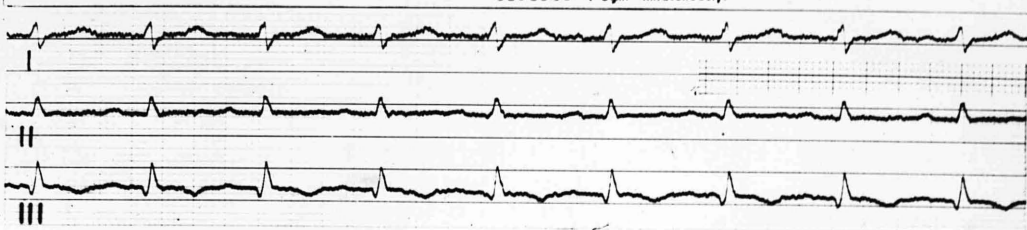
Fig. 26.   Hyperkalaemia in the adrenogenital syndrome.

Patient N.R. aged 21 days.   First salt-losing crisis.
Serum potassium 41 mg./100 ml. (10.5 m. Eq./l.), serum
sodium 239 mg./100 ml. (104 m. Eq./l.), at outset.
First tracing shows chaotic heart action.   Second
and third tracings show the return towards a normal
pattern after treatment.
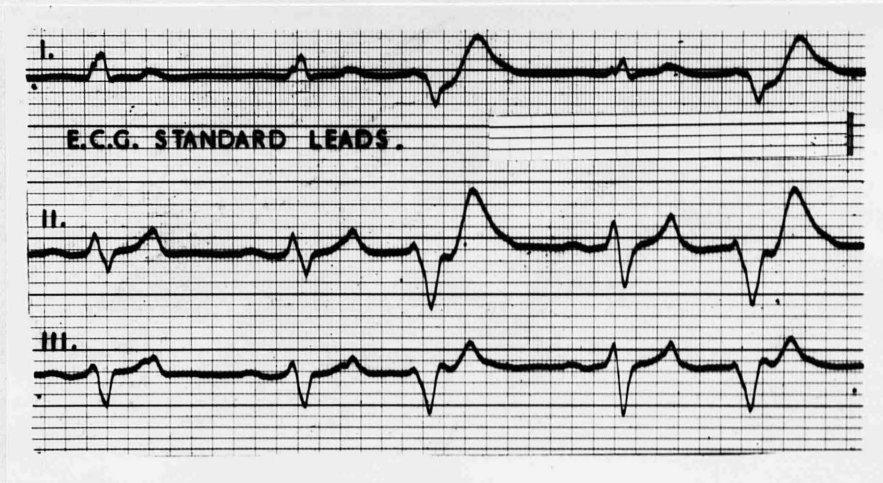
Fig. 27.   Hyperkalaemia in the adrenogenital syndrome.

Patient N.R. aged 23 days.   Second salt-losing
crisis.   Serum potassium 42 mg./100 ml.
(10.8 m. Eq./l.), serum sodium 241 mg./100 ml.
(104.3 m. Eq./l.).   Small R waves, deep S waves,
tall T waves in leads II and III.   Prolonged PR
interval (0.20 second).   Ventricular premature
systoles.
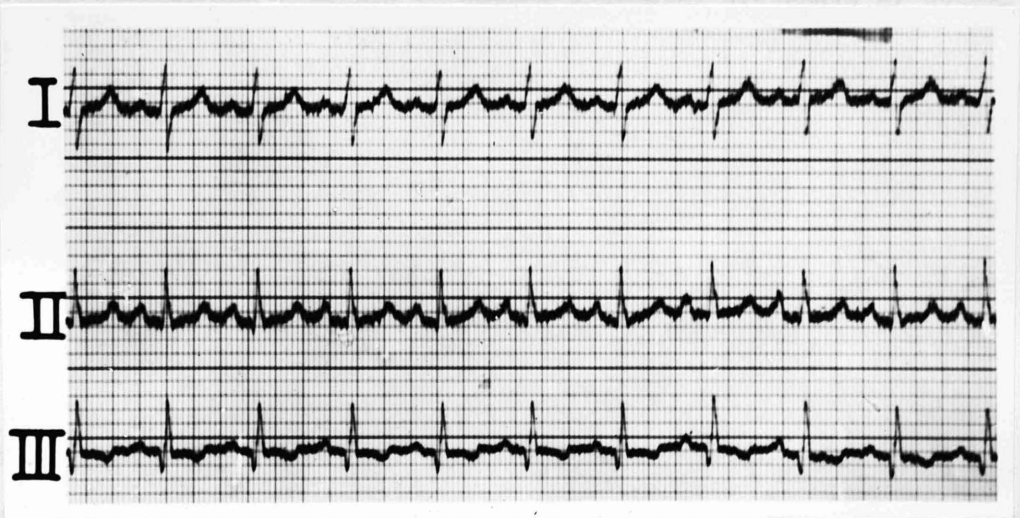
Fig. 28.   Hyperkalaemia in the adrenogenital syndrome.

Patient N.R. aged 26 days.   Serum potassium 42.4 mg./
100 ml. (10.9 m. Eq./l.), serum sodium 243 mg./100 ml.
(105.6 m. Eq./l.).   Electrocardiogram within normal
limits.

ventricular premature systoles.   The PR interval was prolonged
(0.20 second) and the P waves were broad and flat.   This
electrocardiographic picture was considered to be characteristic
of hyperkalaemia.

Intravenous saline and intramuscular cortisone were given and
there was a vast improvement in her clinical condition.   Three
days later however, severe hyperkalaemia (serum potassium 42.4 mg./
100 ml. : 10.9 m.Eq./l.) and hyponatraemia (serum sodium 243 mg./
100 ml. : 105.6 m.Eq./l.) persisted, but on this occasion her
electrocardiogram (Fig. 28) was regarded as being within normal
limits.

<div align="center">D i s c u s s i o n</div>

The electrocardiograms of the first two patients (R.W. and
J.Wi.) showed features accepted as characteristic of hyperkalaemia,
and in both it was possible to make a confident diagnosis of hyper-
kalaemia before the biochemical findings were known.   The
outstanding and indeed pathognomonic feature of these electro-
cardiograms was the tall pointed and rather narrow T wave.   The
extraordinary prominence of this wave was the more obvious when
its height was compared with that of the preceding R wave.

These electrocardiograms were easily interpreted, but this
was not so of those of the third patient (N.R.).   The first of
the series showed a particularly serious disorder of rhythm,
probably/

probably not far removed from ventricular fibrillation, but it is
remarkable that her serum potassium was not so high as that of the
other infant (J.Wi.).   Infant N.R. had more severe hyponatraemia
but that this was not responsible for the extreme changes found in
her first electrocardiogram was indicated by the records obtained
2 and 5 days later.   One showed features in keeping with hyper-
kalaemia, but the other was within normal limits, and yet on each
occasion the serum levels of potassium and sodium were closely
similar to those recorded at the time of the first electrocardio-
gram.   Thus three totally different electrocardiographic pictures
were produced with virtually identical levels of serum potassium
and sodium.

It is clear from this study that the diagnosis of hyperkalae-
mia can in some instances be made from the electrocardiogram, but
that it would be inadvisable to rule out the diagnosis of hyper-
kalaemia on the results of electrocardiographic examination alone.
The examination of the last patient gives grounds for the belief
that the electrocardiogram does not reflect high levels of
potassium in the serum with any accuracy.

<div align="center">

HYPOKALAEMIA

Review of literature

</div>

Whereas the principal electrocardiographic signs of hypocalcaemia

are/

are the opposite of those of pure hypercalcaemia, the signs of hypokalaemia do not apparently bear a similar relationship to those of hyperkalaemia. Nevertheless, in hypokalaemia just as in hyperkalaemia and in disorders of calcium balance attention has been focussed particularly on the components of the ST-T complex.

Wallace and Moll (1949) undertook an electrocardiographic study of a 4 year-old boy with potassium deficiency. They concluded that the characteristic features of the electrocardiogram were depression of the ST segment and flattened or absent T waves. Levine (1954) made reference to the prolonged, flattened T wave which might accompany hypokalaemia but noted that this apparent T wave might have two or even three summits. He likened the T wave with two summits to a silhouette of the Bactrian camel, and the wave with three summits to a rolling countryside.

A valuable study of the lengthened T wave with two summits and of the QT interval in hypokalaemia was made by Lepeschkin and Surawicz (1952). In agreement with Ljung (1950) they concluded that the T wave itself was not lengthened but that there was apparent lengthening because the T wave was immediately followed by a prominent U wave. The corollary of this was that the QT interval and QTc value, measured to the end of the T wave, were not increased but that they would appear to be increased if measurements were to include the U wave. One method which they used/

used to separate the components of the merged TU wave was to record the phonocardiogram at the aortic area simultaneously with the electrocardiogram, and to relate the wave to the second heart sound.   They were of the opinion that the T wave ended at the second sound, and that any wave or part of a wave occurring immediately thereafter was to be accepted as a U wave.

Levine (1954) expressed the opinion that the electrocardiographic signs of hypokalaemia were not directly related to the level of serum potassium.   Gamble, Wiese and Hansen (1948) had earlier described the treatment of an infant with hypokalaemia resulting from prolonged diarrhoea whose serum potassium level returned to within normal limits 5 days before the electrocardiographic signs of hypokalaemia disappeared.   Nadas (1957) was of the opinion that the electrocardiographic changes were more likely to be associated with the intracellular than with the extracellular potassium.   Wallace and Moll (1949) also believed that the absolute level of potassium in the serum had little to do with the electrocardiographic changes but refused to accept that the intracellular concentration of potassium was the critical factor.   They drew attention to the rapidity of the therapeutic effect of potassium in hypokalaemia, and concluded as did Levine (1954) at a later date that the critical factor as far as the electrocardiographic and therapeutic effects of potassium were concerned might be the concentration of potassium at the surfaces

of/

of cells. This hypothesis is attractive but it lacks proof. If the experimental work of Mazia (1940) on the Elodea cell were to prove applicable to the human cell, it would seem that the binding of an ion by a cell surface depends not simply upon its absolute concentration in the extracellular fluid but on its exact quantitative relationship to other ions in that fluid.

There is at least one other possible explanation for a lack of correlation between the extracellular concentration of potassium and the electrocardiographic features. Rodriguez, Wolfe and Bergstrom (1950) and Perkins, Petersen and Riley (1950) found myocardial lesions ("hypokalaemic myocarditis") in patients who suffered from potassium deficiency before death. One was a 2 year-old boy (Rodriguez et al. 1950) who had been treated for diabetic coma. It is conceivable therefore, although proof would be virtually impossible to obtain, that the slow resolution of the electrocardiographic features of hypokalaemia might in some cases be due to residual myocardial damage.

Clinical material

Electrocardiograms of 4 patients are to be described. In 2 of these potassium deficiency occurred during the treatment of gastro-enteritis, in 1 during the treatment of adrenocortical failure and in the other during the treatment of diabetic coma.

Clinical, biochemical and electrocardiographic
findings/

Clinical, biochemical and electrocardiographic

findings

Patient 1

M.C. was admitted to the Royal Hospital for Sick Children
at the age of 11 months.   Four days earlier she began to vomit
and to have profuse diarrhoea.   After 3 days, vomiting ceased and
during the last 24 hours before admission she was given by mouth
3.5 litres of half-strength Ringer-lactate solution (containing
sodium lactate and chloride, potassium chloride and calcium
chloride).

On admission she was gravely ill.   She was dehydrated and
fevered, and profuse diarrhoea persisted.   During the next 18
hours she was given 1.2 litres of half-strength lactate-saline
(0.45% NaCl, M/40 sodium lactate).   She became less dehydrated,
but she remained pale and limp, and was extremely drowsy.
Potassium deficiency was suspected and chemical analysis supplied
the proof.   The serum potassium was only 9.7 mg. per 100 ml.
(2.5 m.Eq./l.).   In addition there was hypocalcaemia (serum
calcium 8.4 mg./100 ml.), and a severe metabolic acidosis.   The
electrocardiogram (Fig. 29) showed what appeared to be a broad
shallow T wave and a lengthened QT interval (QTc 0.47) without
lengthening of the ST segment (not greater than 0.08 second).
This apparent T wave did not have two summits to suggest the
presence of a U wave.   Nevertheless the electrocardiogram was
considered to support the diagnosis of hypokalaemia.   The ST
segment was not unduly long and no indication was therefore given
of the low total serum calcium perhaps because the metabolic
acidosis had increased the ionized fraction.   Nevertheless it
seemed obvious that the electrocardiographic signs of hypokalaemia
might be confused with those of hypocalcaemia if there were diffi-
culty/
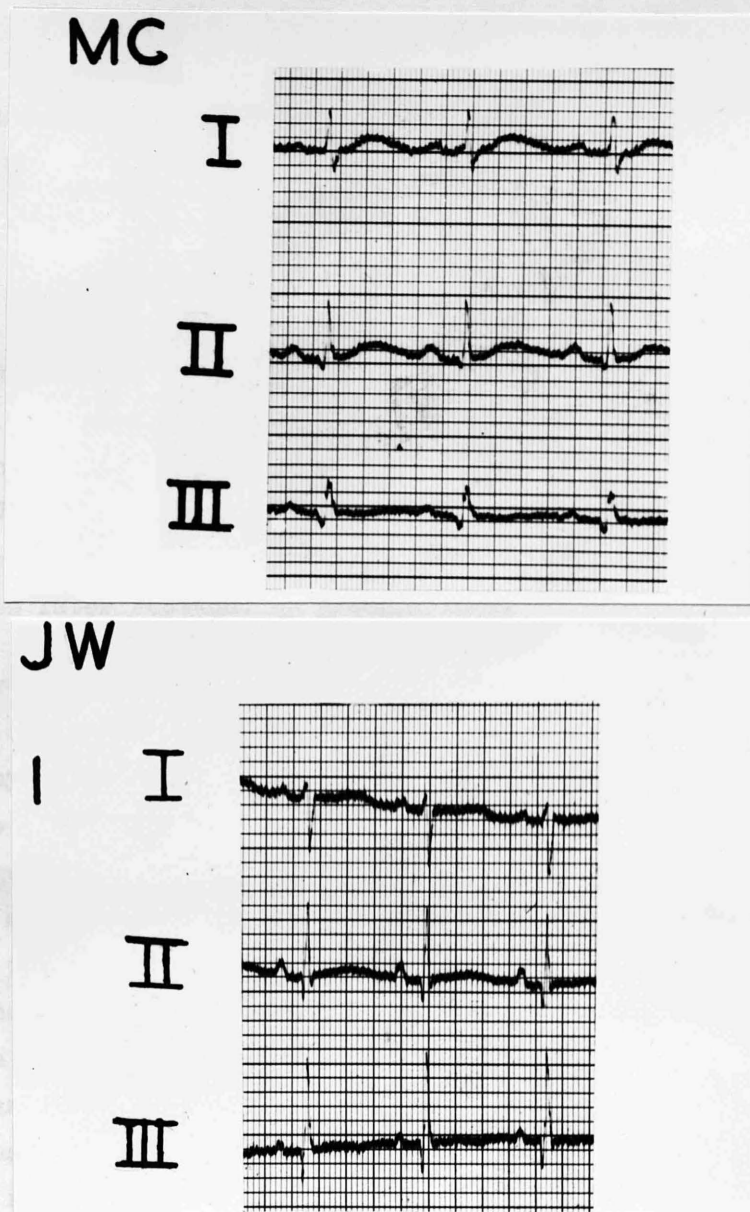
Fig. 29. Hypokalaemia during treatment of gastro-enteritis.

Patient M.C. aged 11 months.   Serum potassium 9.7 mg./100 ml. (2.5 m. Eq./l.).   Broad T or TU wave and lengthening of apparent electrical systole (QTc 0.47).   ST segment not lengthened.

Comparison of this electrocardiogram with that of patient J.W. taken when the serum calcium was 8.3 mg./100 ml. shows that it may be difficult to distinguish the electrocardiographic changes of hypokalaemia from those of hypocalcaemia.

culty in determining the point at which the ST segment ended and a shallow T wave began (Fig. 29).

Patient 2

R.W. is the 11 year-old girl with renal and adrenal tuberculosis already referred to in connexion with the hyperkalaemia which was caused by adrenocortical failure (page 160 and Fig. 24). She was given glucose-saline intravenously for 24 hours (3.8 litres with 45 grams NaCl), and thereafter saline by mouth. D.C.A. and adrenal cortical extract (Eucortone) were given at first, but cortical extract was later replaced by prednisolone.

After 48 hours her clinical state was enormously improved. The serum sodium and chloride had risen but hypokalaemia had replaced hyperkalaemia (serum potassium 11 mg./100 ml. : 2.8 m.Eq./ l.). The electrocardiogram (Fig. 30) showed a broad TU wave of low voltage. The components of this double wave were easily seen in lead I and for this reason it was possible to calculate from that lead the true QTc value. This was not increased (QTc 0.37) whereas the apparent QTc value in lead II, in which the T and U waves were fused, was increased (QTc 0.585). During the next 24 hours potassium chloride was given 4 hourly and the electrocardio- gram gradually reverted to a normal pattern, but the serum potassium remained low (12 mg./100 ml. : 3.1 m.Eq./l.).

One hour after the first dose of potassium chloride, a small U wave was still visible following closely upon the T wave. An attempt was made to relate these waves to the second heart sound at the aortic area (Fig. 31). The phonocardiogram showed that the first and larger wave (T wave) ceased with the second sound and that the second and much smaller wave (U wave) occurred immediately after the sound.

Patient 3/
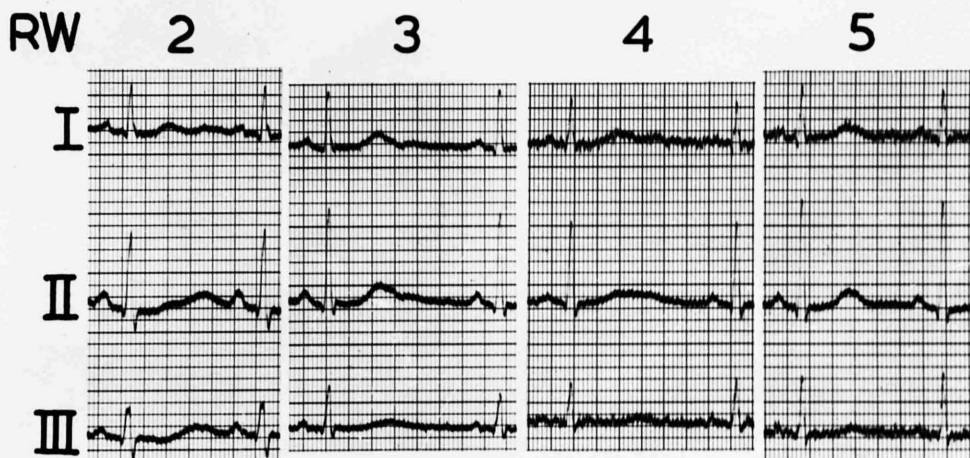
Fig. 30. Hypokalaemia during treatment of adrenal cortical failure.

Patient R.W. aged 11 years.   See Fig. 24 for record R.W.1. (hyperkalaemia).

Record R.W.2.   Serum potassium 11 mg./100 ml. (2.8 m. Eq./l.). Low voltage TU waves. Actual QTc (lead I) 0.37 but apparent QTc (lead II) 0.585.

Record R.W.3.   One hour after 2G of KCl. Small U wave still visible. See Fig. 31.

Record R.W.4.   After 8G of KCl. Serum potassium 13 mg./100 ml. (3.3 m. Eq./l.). Broad, low TU wave in lead II; separate T and U waves in lead I.

Record R.W.5.   After 16G of KCl. Serum potassium 12 mg./100 ml. (3.1 m. Eq./l.). Normal T wave.   Normal QTc (0.405).
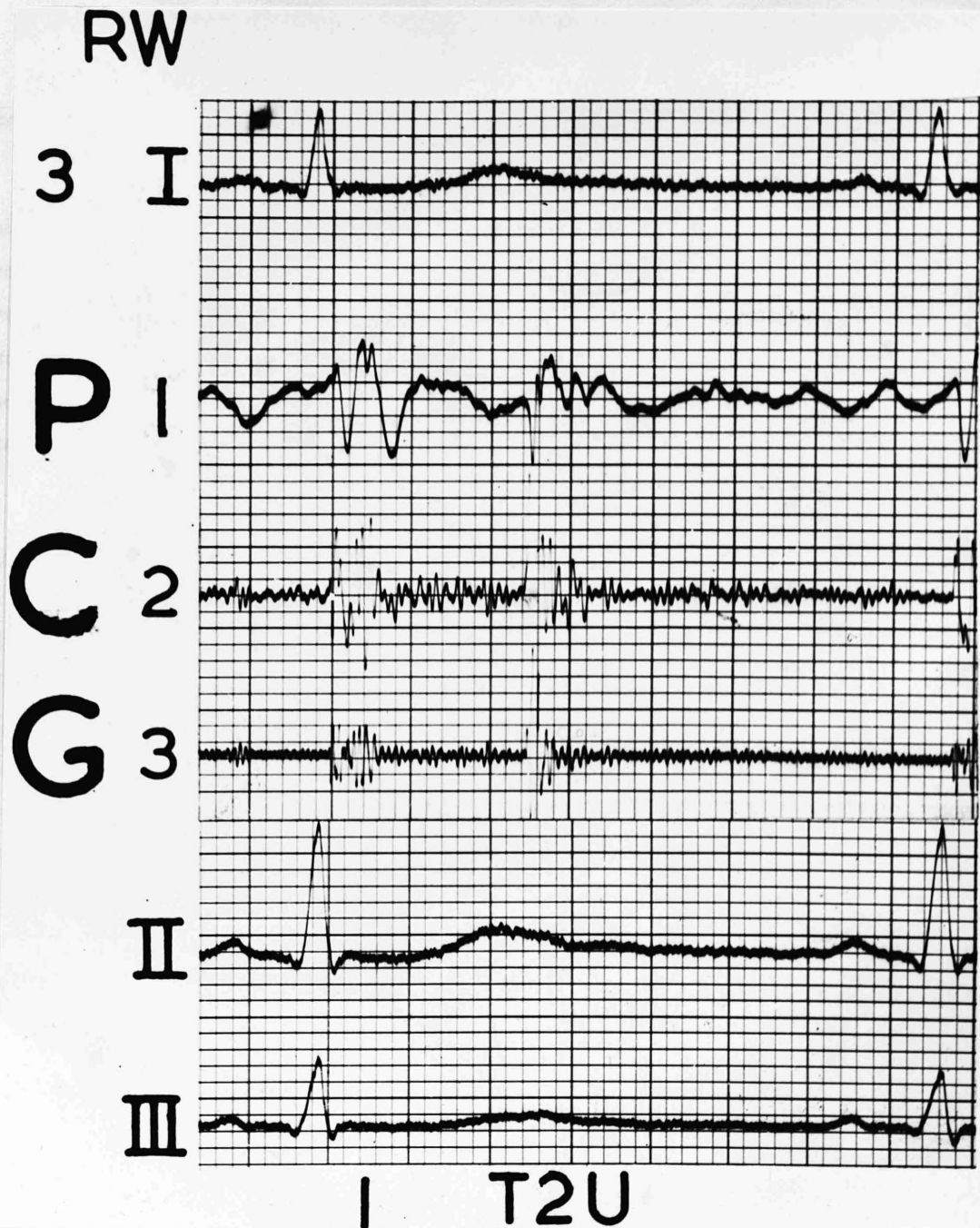
Fig. 31. Hypokalaemia during treatment of adrenal cortical
failure.

Patient R.W. Composite representation of phono-
cardiogram at aortic area and electrocardiogram
(Fig. 30. R.W.3.) showing relationship of the T
wave and a small U wave (leads II and III) to the
second heart sound. The first and second heart
sounds are represented on the abscissa by the
numerals 1 and 2.

Patient 3

J.T., a girl aged 14 months, was admitted to hospital in diabetic coma. She had been unduly thirsty for 4 weeks, and 7 days before admission she began to vomit. She became drowsy, developed acidotic breathing and on the day of admission became unconscious. On admission she was severely dehydrated. The blood sugar was 457 mg. per 100 ml. and there was glycosuria and ketonuria.

During the first 18 hours of treatment she was given 165 units of soluble insulin, and 1.5 litres of fluid of which 1 litre was given by intravenous infusion as half-strength saline (0.45% NaCl) with 5% glucose and M/40 sodium lactate. The blood sugar fell to 95 mg. per 100 ml., the ketonuria decreased and the signs of dehydration receded. She regained consciousness, but remained drowsy and limp with hypotonicity of muscles and marked abdominal distension. On clinical grounds she was judged to be suffering from potassium depletion and this was confirmed by electrocardiography (Fig. 32). Because of the relative inaccessibility of veins it was decided to use electrocardiographic rather than biochemical control during treatment. She was given 1 gram of potassium chloride by mouth at 4 hourly intervals. The electrocardiogram showed a gradual disappearance of the abnormal features and 96 hours later when 24 grams had been given it was within normal limits. During this time the patient made an uninterrupted clinical recovery.

In the earliest electrocardiograms the most striking feature was a long wave of low amplitude in the position of the T wave. There was no evidence that this wave was composed of fused T and U waves but in the light of previous experience (Fig. 30) it is probable/
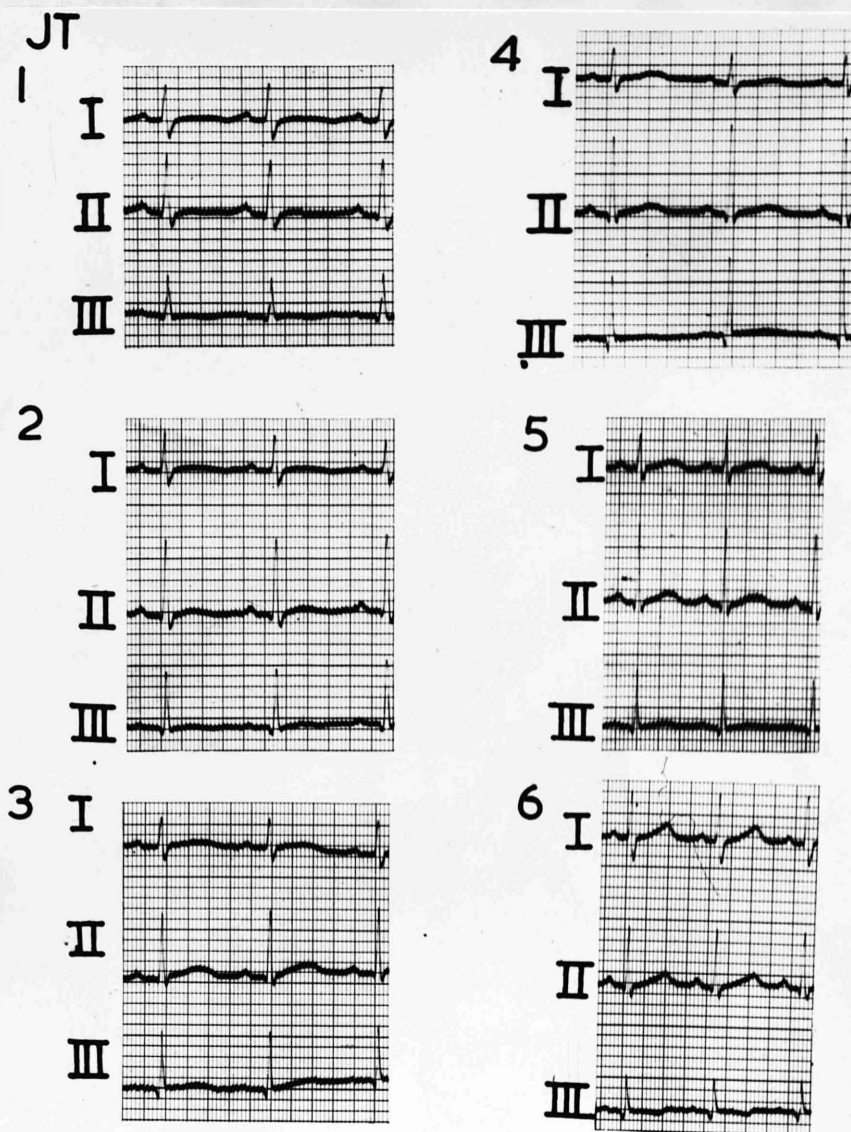
Fig. 32. Hypokalaemia during treatment of diabetic coma.

Patient J.T. aged 14 months. This series of electrocardio-
grams shows the gradual return of the ST-T complex to a normal
contour during the course of treatment with potassium chloride.

1. Before administration of KCl. Long flat TU wave. Apparent
   QT interval is prolonged (Apparent QTc = 0.455).
2. After 4 hours. Total dose of KCl: 1G. Apparent QTc = 0.415.
3. After 24 hours. Total dose of KCl: 6G. Apparent QTc =
   0.41.
4. After 30 hours. Total dose of KCl: 8G. Apparent QTc =
   0.395.
5. After 48 hours. Total dose of KCl: 12G. Apparent QTc =
   0.39.
6. After 96 hours. Total dose of KCl: 24G. Apparent QTc =
   0.40.
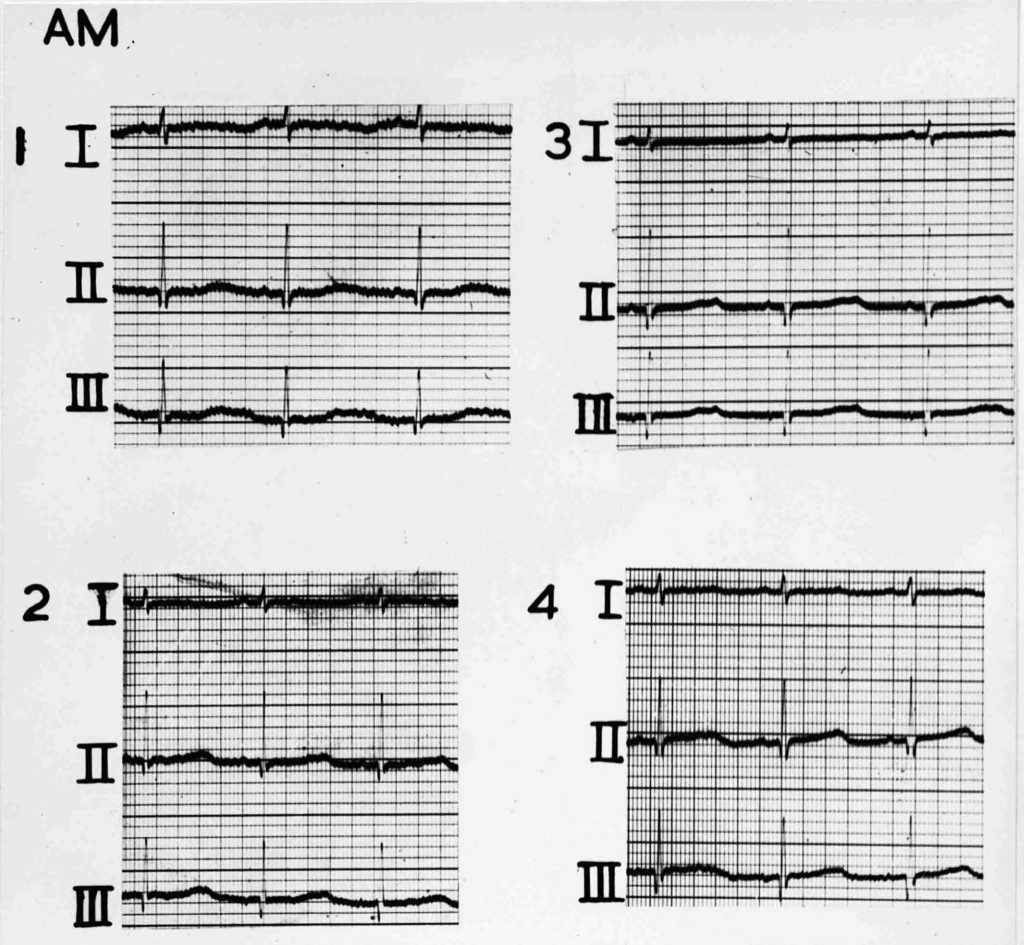
Fig. 33.   Hypokalaemia during treatment of gastro-enteritis.

Patient A.M. aged 8 weeks. This series shows slow regression of electrocardiographic signs.

1. Serum potassium 11.8 mg./100 ml. (3.02 m.Eq./l.).
   Broad TU wave of low voltage. Apparent QTc 0.60.

2. After 0.6G. of KCl.   Similar appearance.
   Apparent QTc 0.50.

3. After 0.9G of KCl. Serum potassium 23.6 mg./100 ml.
   (6 m.Eq./l.). Little change except for further
   shortening of apparent QTc (0.47).

4. Forty-eight hours after Record 3. Further
   improvement in electrocardiogram but apparent
   QTc still prolonged (0.445).

probable that this was the case. The apparent QTc value was increased (QTc 0.455) on account of the length of this wave and not, in contrast with the state of affairs in hypocalcaemia, on account of a lengthened ST segment. The length of the T or TU wave gradually decreased, it gained in height and the apparent QTc value declined.

Patient 4

This last patient is described because of the slow regression of the electrocardiographic changes after the serum potassium had returned to a normal level (Fig. 33).

A.M., a premature infant, was admitted to hospital at the age of 8 weeks suffering from severe gastro-enteritis. She weighed 1.575 kg. ($3\frac{1}{2}$ lbs.), and was severely dehydrated. She was given an intravenous infusion of quarter-strength saline (0.225% NaCl) with 5% glucose. At the end of 30 hours, after having received 720 ml. of fluid, she was enormously improved but still had profuse diarrhoea. The serum potassium was 11.8 mg. per 100 ml. (3.02 m.Eq./l.), and the electrocardiogram showed considerable lengthening of the apparent QT interval (QTc 0.60), with a broad shallow T or TU wave.

Potassium chloride was given by mouth in doses of 0.3 gram 6 hourly. After 2 doses the electrocardiogram showed evidence of improvement inasmuch as the apparent QT interval had decreased in length (QTc 0.50). After 3 doses, the serum potassium had risen to 23.6 mg. per 100 ml. (6 m.Eq./l.), but further improvement in the electrocardiogram was only slight; the T waves were still flattened and the apparent QT interval was still prolonged (QTc 0.47). Further electrocardiograms taken during the following 72 hours showed a gradual return of the record to a normal pattern.

D i s c u s s i o n

The electrocardiograms of 4 patients suffering from potassium depletion/

depletion have been studied with particular reference to that part of the record following the QRS complex. In some electrocardiograms of one patient (R.W.) the T wave was seen to be immediately followed by a U wave. In other electrocardiograms of this and other patients the T wave itself appeared to be lengthened but it is likely that this broad wave represented the fusion of a U wave with the T wave. In those instances in which there was a broad T or TU wave the apparent QTc value was increased because of this wave and not, as in hypocalcaemia, because of a lengthened ST segment. When it was possible to separate the U wave from the T wave the true QTc value could be measured and was found not to be increased. This broad wave was of low amplitude, and during treatment with potassium chloride not only did the apparent QTc value decrease because of the disappearance of the U wave, but the amplitude of the T wave increased.

In one patient (R.W.) the abnormal features disappeared while the serum potassium was still low, but in another (A.M.) they persisted even after the serum potassium had risen to a normal level. This evidence lends support to the contention of Wallace and Moll (1949) and of Levine (1954) that the electrocardiographic signs are not dependent upon the concentration of extracellular potassium _per se_. Nevertheless the examination of another patient (J.T.) showed that serial electrocardiography can provide valuable information during the treatment of potassium deficiency.

It/

It is not surprising that the electrocardiogram fails to reflect the serum concentration of potassium. Potassium is essentially an intracellular cation and, as mentioned in my review of the biochemical background to these investigations, the serum level in some diseases may give little indication of the true state of the potassium balance. It can scarcely be disputed that these electrocardiographic signs are caused by potassium depletion, but the precise mechanism of their production is as yet undetermined. For the present this term, potassium depletion, seems a more correct description for the disorder which these signs represent than hypokalaemia by which is implied merely a decrease in the potassium content of the plasma.

HYPERNATRAEMIA

Purpose of investigation and clinical material

Reference has been made to the opinion of Levine and his colleagues (1952) that the effect on the electrocardiogram of hyperkalaemia is in part related to the level of serum sodium. If hyponatraemia is present the electrocardiographic signs of potassium intoxication are said to appear when the serum potassium is less highly elevated than when the serum sodium is within normal limits. This finding might imply that the concentration of sodium in the extracellular fluid could exert a direct effect on the electrocardiogram, and that in producing such an effect sodium might/

might act as an antagonist of potassium (Massie and Walsh 1960).
With this possibility in mind electrocardiograms were obtained
from 3 patients suffering from hypernatraemic dehydration.   Hypo-
kalaemia accompanied this disorder in two instances.

<div align="center">Clinical, biochemical and electrocardiographic</div>

<div align="center">findings</div>

Patient 1

A.S., a 19 month old child, suffered from phenylketonuria
with severe mental retardation (phenylpyruvic oligophrenia).
While undergoing treatment with a diet containing little phenyl-
alanine she became acutely ill with an infection of the respira-
tory tract.   The special diet was discontinued and she was given
fruit juices with glucose added.   She vomited persistently for
36 hours, and when examined thereafter she was dehydrated and
extremely limp.   She was thought to be suffering from potassium
depletion.   Estimation of the serum potassium supported this
view (12.8 mg./100 ml. : 3.3 m.Eq./l.), but she was found also to
have pronounced hypernatraemia (serum sodium 436 mg./100 ml. :
190 m.Eq./l.).   There was a slight increase in plasma chloride
and serum calcium, probably attributable to haemoconcentration
from dehydration.   The increase in serum sodium concentration
was too great to be accounted for merely by dehydration but might
possibly have had some connexion with the cerebral disorder of
phenylketonuria (Cooper and Crevier 1952).

The electrocardiogram did not show any change which suggested
hypokalaemia (Fig. 34).   There was marked sinus tachycardia
(220/minute), with partial augmentation of the T and P waves.
The/
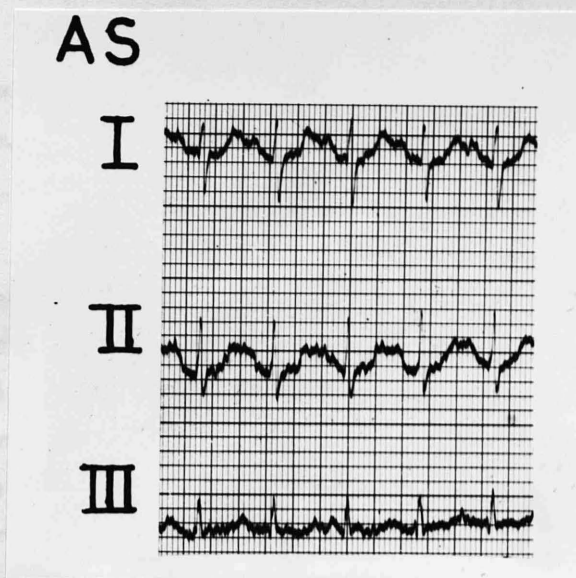
Fig. 34. Hypernatraemia and hypokalaemia.

Patient A.S. aged 19 months. Serum sodium 436 mg./100 ml. (190 m.Eq./l.), serum potassium 12.8 mg./100 ml. (3.3 m.Eq./l.). Sinus tachycardia (220 per minute). Partial augmentation of P and T waves. QTc not greater than 0.39. No electrocardiographic evidence of hypokalaemia.
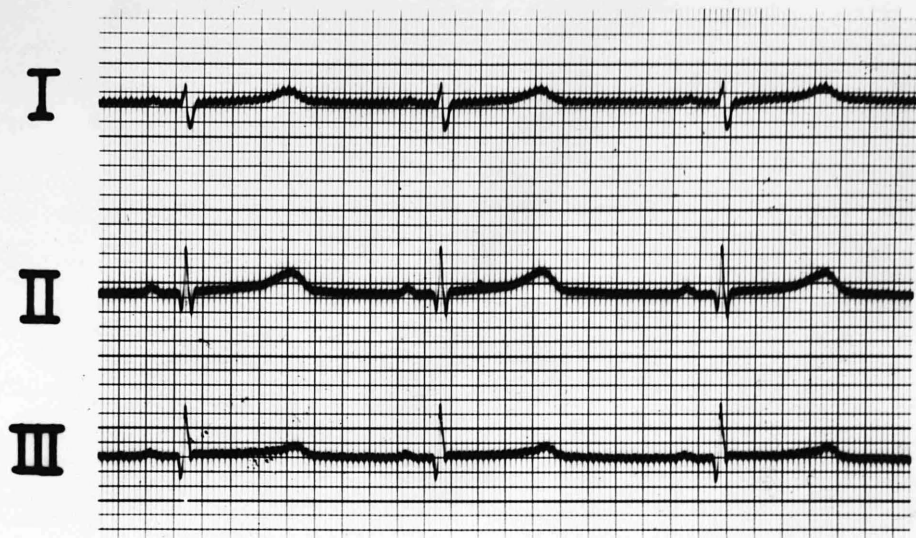
Fig. 35. Hypernatraemia and hypocalcaemia.

Patient H.D. aged 5 weeks. Serum sodium 382 mg./100 ml. (166 m.Eq./l.), serum calcium 8.9 mg./100 ml., serum potassium 25.8 mg./100 ml. (6.5 m.Eq./l.). Sinus bradycardia (average rate 60 per minute) and sinus arrhythmia. ST segment (0.26 second) and QT interval (QTc 0.48) prolonged.

The T wave was not low or broad, and the QT interval did not seem to be prolonged (QTc less than 0.39).

Patient 2

H.D. was 5 weeks old when he was transferred to the Royal Hospital for Sick Children suffering from gastro-enteritis. There had been profuse diarrhoea and frequent vomiting for 12 days. He was moribund on admission, and he died on the following day. At autopsy thrombosis of the right renal vein and of the right transverse cerebral sinus was found.

At admission there was widespread sclerema as well as pitting oedema. He was unconscious and had head retraction. The clinical impression of hypernatraemia was confirmed by biochemical investigation (serum sodium 382 mg./100 ml. : 166 m.Eq./l.). There was in addition a severe metabolic acidosis (plasma total CO_2 16.6 volumes /100 ml. : 7.4 m.Eq./l.). The serum calcium was low (8.9 mg./100 ml.) and the potassium raised (25.8 mg./100 ml. : 6.5 m.Eq./l.).

The electrocardiogram (Fig. 35) showed sinus bradycardia (average rate 60 per minute) and sinus arrhythmia. The QT interval was prolonged (QTc 0.48) and this was caused by an exceedingly long ST segment (0.26 second) whose lengthening seemed too great to be due to bradycardia alone. On these grounds the electrocardiogram was interpreted as being diagnostic of hypocalcaemia.

Patient 3

M.D. was admitted to hospital at the age of 11 days. He had been healthy until the ninth day but then began to pass loose stools/

stools.   On admission he was severely dehydrated and hypothermic
(rectal temperature 92°F).   He had profuse diarrhoea and gastro-
enteritis was diagnosed.   Quarter-strength saline (0.225% NaCl)
with M/40 sodium lactate was given by mouth.   Diarrhoea persisted
but there was some immediate improvement in his general condition.
Three days later however he seemed unduly limp, and because it was
thought that he might be suffering from potassium depletion
biochemical and electrocardiographic examinations were undertaken.
The serum potassium was low (13.3 mg./100 ml. : 3.4 m.Eq./l.).
There was a severe metabolic acidosis (plasma CO_2 9.1 volumes/100
ml. : 4.1 m.Eq./l., plasma chloride 436 mg./100 ml. : 124.5 m.Eq./
l.).   Both the serum sodium (311 mg./100 ml. : 135.3 m.Eq./l.) and
the serum calcium (11.4 mg./100 ml.) were regarded as being within
normal limits.   The electrocardiogram (Fig. 36) was bizarre and
showed first degree atrio-ventricular block (PR 0.15 second),
bundle branch block (QRS 0.11 second) and a QT interval within
normal limits but without a detectable ST segment (QTc 0.40).

Potassium and sodium bicarbonate were given by mouth together
with small feeds of milk and quarter-strength saline with sodium
lactate.   The diarrhoea persisted and in 24 hours he had not
improved.   Hypernatraemia was now present (serum sodium 346 mg./
100 ml. : 150.5 m.Eq./l.).   The metabolic acidosis persisted
although the plasma CO_2 had almost doubled (17.4 volumes/100 ml. :
7.8 m.Eq./l.).   The serum potassium though still low had risen to
15.8 mg. per 100 ml. (4.1 m.Eq./l.).   The electrocardiogram (Fig.
36) had altered slightly.   The PR interval (0.13 second) had
shortened and was within normal limits.   The QRS complex (0.09
second) had shortened, but was still unduly long.   The QTc value
(0.41) had increased and an ST segment was now visible.   The
contour of the QRS complex remained abnormal.   The contour of the
P/
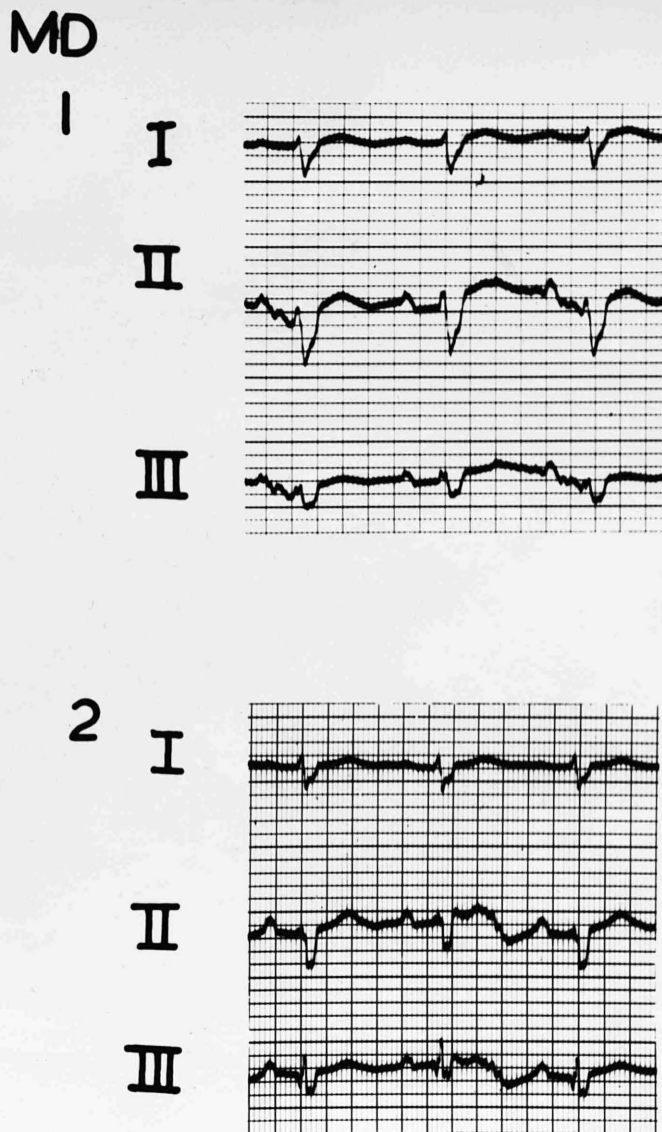
Fig. 36. Hypernatraemia during treatment of gastro-enteritis.

Patient M.D. aged 14 days.

E.C.G. 1. Serum sodium 311 mg./100 ml. (135.3 m.Eq./l.), serum potassium 13.3 mg./100 ml. (3.4 m.Eq./l.), serum calcium 11.4 mg./100 ml. First degree A-V block (PR 0.15 second), bundle branch block (QRS 0.11 second), QT interval within normal limits (QTc 0.40) but no ST segment visible.

E.C.G. 2. Serum sodium 346 mg./100 ml. (150.5 m.Eq./l.), serum potassium 15.8 mg./100 ml. (4.1 m.Eq./l.). PR interval (0.13 second) and QRS complex (0.09 second) shorter. QT interval within normal limits (QTc 0.41). ST segment now visible.

P waves in leads II and III of both electrocardiograms suggested right atrial hypertrophy. The onset of hypernatraemia did not appear to have been attended by the appearance of any new abnormality in the electrocardiogram.

Sodium was witheld and potassium bicarbonate continued, but diarrhoea persisted and the infant died next day. Autopsy revealed widespread atrophy of myocardial fibres in addition to severe ileocolitis. The cause of the myocardial lesion was undetermined.

D i s c u s s i o n

I have thought it advisable to defer until last any consideration of the electrocardiographic findings in patients suffering from hypernatraemia, because it is apparent from published accounts that hypernatraemia tends not to be an isolated biochemical disorder, but merely additional to a severe disorder already in existence (Finberg and Harrison 1955, Weil and Wallace 1956). It is likely therefore to be difficult to define with certainty the electrocardiographic signs, if any, for which hypernatraemia itself is responsible.

Hypocalcaemia has been reported in association with hypernatraemia (Finberg and Harrison 1955), and in the electrocardiogram of H.D., who suffered from hypocalcaemia, were found the long ST segment and QT interval (QTc) characteristic of this disorder. This is surprising because the hypocalcaemia was not severe, and the ionized fraction upon which the electrocardiographic changes are/

are thought to depend, might have been expected to be substantially increased by reason of the metabolic acidosis. This patient also had a raised serum potassium without any electrocardiographic sign of hyperkalaemia, but in view of his history of persistent diarrhoea it is likely that the serum level did not reflect the true state of the total body potassium which might have been expected to be depleted rather than in excess.

Defects in conduction were reflected in the electrocardiograms of the third patient (M.D.) by a long PR interval in one and by bundle branch block in both; these changes can probably be ascribed to the myocardial lesion subsequently found at autopsy. The absence of an ST segment in the first electrocardiogram may have been evidence of hypercalcaemia; the serum total calcium was not increased (11.4 mg./100 ml.), but it is likely that the severe metabolic acidosis had led to an increase in the ionized component. Comparison of the electrocardiogram recorded after the onset of hypernatraemia with that recorded beforehand did not reveal that any new feature had appeared which could also be found in the electrocardiograms of the other patients.

It seems unlikely that hypernatraemia has any important effect on heart rate since the patient with the highest serum sodium (A.S.) had sinus tachycardia, but another (H.D.) had sinus bradycardia.

No/

No other significant abnormality was present in these electrocardiograms, and one must therefore conclude that no signs were detected which could be regarded as caused by hypernatraemia.

Two patients (A.S. and M.D.) suffered also from hypokalaemia, but in neither was there any suggestion of the fused TU wave of low voltage characteristic of potassium deficiency. There is therefore no evidence to suggest that hypernatraemia potentiates the electrocardiographic effect of hypokalaemia, and although the converse association has been reported (the potentiation of the hyperkalaemic effect by hyponatraemia) there is no reason to suppose that sodium and potassium are antagonistic with regard to their influence on the electrical activity of heart muscle.

CONCLUSIONS/

CONCLUSIONS

Hypocalcaemia

A study of 3 newborn infants lends support to the view that the principal electrocardiographic effect of hypocalcaemia is to lengthen the ST segment and thus to increase the length of the QT interval (QTc). The signs of hypercalcaemia (idiopathic hyper-calcaemia of infancy excepted) are the converse of these. It may be concluded therefore that serum calcium levels from very low to very high find expression in the electrocardiogram as points in a continuum extending from a very long to a very short ST segment and QT interval (QTc).

The recognition of slight lengthening of the QT interval (QTc) due to mild hypocalcaemia is impossible in the first days of life because healthy infants may have very long QT intervals resulting from peculiarly long T waves.

The length of the ST segment affords a more reliable indication of hypocalcaemia, but insufficient is known of normal values for this to be used with assurance in the differential diagnosis of convulsive disorders in the first days of life.

No support can be given for the view that a tall pointed T wave is a feature of the electrocardiogram in hypocalcaemia.

Hyperkalaemia/

Hyperkalaemia

It is concluded from the examination of a newborn infant and of an older child that the most striking sign of hyperkalaemia is a tall pointed T wave. The configuration of the QRS complex may be altered and the PR interval lengthened.

It is concluded from the examination of another infant that the electrocardiographic diagnosis of hyperkalaemia can be difficult if not impossible, and that the signs do not reflect the serum potassium level with any accuracy. This discrepancy in the electrocardiographic reflection of the serum potassium cannot be explained on the grounds of changes in serum sodium concentration.

Hypokalaemia

The electrocardiographic signs of hypokalaemia are not the converse of those of hyperkalaemia, but the principal signs are once more found in the neighbourhood of the T wave. The T wave is of low voltage and it may seem exceptionally broad, as it did in the electrocardiograms of three patients. It is concluded however from the examination of another patient that this broad wave is composed of a T wave immediately followed by a prominent U wave. The QT interval (QTc) only appears to be lengthened if the U wave is mistakenly included in the measurement of the interval.

The electrocardiographic differentiation of potassium from calcium/

calcium depletion may prove difficult if the ST segment merges imperceptibly with the ascending limb of a fused TU wave of low voltage. Under these circumstances there may be nothing to indicate whether the ST segment or a TU wave is responsible for apparent lengthening of the QT interval (QTc).

Absence of direct correlation between the level of serum potassium and the electrocardiographic signs of hypokalaemia has been shown, but this observation is not held to invalidate the electrocardiographic assessment of potassium deficiency. Potassium is essentially an intracellular cation, and it is therefore not unreasonable to suspect that the electrocardiographic signs more closely reflect the total body potassium than does the serum potassium level.

Hypernatraemia

No uniformity existed among the electrocardiographic features of 3 infants suffering from hypernatraemia. In none however did hypernatraemia occur as an isolated biochemical disorder.

Hypokalaemia accompanied hypernatraemia in 2 patients but in neither did the electrocardiogram indicate potassium deficiency. There is therefore no evidence to suggest that the potentiating effect which hyponatraemia is reported to exert on the electrocardiographic response to hyperkalaemia is to be regarded as an expression of a general antagonism between sodium and potassium in relation to the electrical events of the cardiac cycle.

Electrocardiography in Idiopathic Hypercalcaemia and Other Cation Disorders of Childhood

Page

ELECTROCARDIOGRAPHY IN IDIOPATHIC HYPERCALCAEMIA AND OTHER CATION DISORDERS OF CHILDHOOD

ENVOI

It is now possible to make a concluding statement as to the significance of these investigations. Although digressing into the realm of pathology, their main purpose was to enquire into the place of electrocardiography in the diagnosis of the cation disorders of childhood.

It is clear that in idiopathic hypercalcaemia of infancy electrocardiography cannot replace the chemical determination of the serum calcium, for the findings in this disease run counter to those in simple hypercalcaemia from other causes. The specific findings in idiopathic hypercalcaemia do however contribute to the diagnosis, and raise an interesting problem as to the role of vitamin D in their pathogenesis. The apparent specificity of these electrocardiographic signs is such that their presence together with a raised serum calcium points to a diagnosis of idiopathic hypercalcaemia of infancy or of vitamin D poisoning.

There/

There is no doubt that during the treatment of hypocalcaemia electrocardiography can provide evidence of an increase in serum calcium, but one has to record that in the neonatal period, at least, it cannot be relied upon to give clear evidence of mild hypocalcaemia.   One general conclusion which can be drawn from the examination of infants with disorders of calcium balance is that for the detection of significant changes in the time intervals of the electrocardiogram, adequate standards derived from healthy infants are essential because of the profound influence which age and heart rate exert upon the electrocardiogram in infancy.

It is perhaps in potassium depletion that electrocardiography gives the most useful diagnostic information, and this is of especial value in infancy because the result is not only rapidly available but is obtained with less disturbance to the patient than is entailed by the removal of a sample of blood.   One might go so far as to suggest that the electrocardiographic signs may give more dependable evidence of potassium depletion than is possible from the determination of the serum level of a cation which is preponderantly intracellular in its distribution.   There is less evidence to suggest that electrocardiography is of such diagnostic value in potassium intoxication, but here again the possibility cannot be ruled out that the electrocardiographic signs are more closely dependent upon the total body potassium than/

than upon the extracellular potassium, as reflected by the serum level. Electrocardiography does not appear however to have any place in the diagnosis of hypernatraemia.

Although the electrocardiogram is clearly no substitute for the estimation of serum levels of the cation in question, it nevertheless can in certain conditions provide reliable confirmatory evidence of cation imbalance and is a valuable addition to the diagnostic procedures in this complex and important field of medicine.

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ELECTROCARDIOGRAPHY IN IDIOPATHIC

HYPERCALCAEMIA AND OTHER CATION

DISORDERS OF CHILDHOOD

SUMMARY

Electrocardiograms of 100 healthy infants aged from 2 weeks
to 12 months were recorded and analysed in order to provide standard
measurements for comparison with those made in electrocardiograms
of infants suffering from idiopathic hypercalcaemia and other
disorders of cation balance.   The conclusions of this investiga-
tion may be summarized as follows:-

1.   The heart rate falls as age increases.   The rate lay between
      207 and 102 per minute in this series.

2.   The P wave, PR interval, QRS complex and T wave lengthen as
      age increases, independently of heart rate.

3.   The PR interval, QRS complex and T wave lengthen as the heart
      rate falls, independently of age.

4.   The ST segment shortens as age increases, and lengthens as the
      heart rate falls.

5.   The QT interval lengthens as the heart rate falls.   The
      influence of heart rate is so profound that it is necessary
      to apply a correction to the measured QT interval to permit
      comparisons between QT intervals recorded at different heart
      rates.   The corrected QT interval is referred to as the QTc
      value.

6./

6. Time intervals in this series of healthy infants have the
    following minimum and maximum values:

P wave	0.04–0.08 second	T wave	0.09–0.15 second
PR interval	0.08–0.14 second	ST segment	0.05–0.11 second
QRS complex	0.05–0.08 second	QT interval	0.21–0.29 second

QTc value 0.36–0.42.

Electrocardiograms of 25 patients with idiopathic hypercalcae-
mia were recorded. Certain features were compared with those of
healthy subjects, and with those of 3 newborn infants with hyper-
calcaemia caused by the injection of calcium gluconate during
replacement transfusion. The conclusions of this investigation
may be summarized as follows:-

1. Newborn infants with hypercalcaemia have a shortened ST
    segment and a decrease in the QTc value.

2. In patients with idiopathic hypercalcaemia, hypercalcaemia is
    accompanied by a shortened ST segment, but not by a decrease in
    the QTc value because of the undue length of the T wave. The
    QTc value cannot therefore be used to give an indication of the
    serum calcium level.

3. In idiopathic hypercalcaemia the contour of the ST-T complex
    is often abnormal with a prominent broad flat-topped T wave,
    which is not directly related to the level of serum calcium.

4. The abnormal contour of the ST-T complex in idiopathic
    hypercalcaemia may reflect interference with myocardial
    activity either by a heart lesion caused by vitamin D, or by
    the/

the action of a chemical substance associated with it.

An animal experiment was conducted in order to gain information concerning heart lesions caused by vitamin D. Vitamin D_3 and vitamin D_2 were each given to 9 young rabbits and there were 9 controls. A study was made of the pathological changes in the heart and aorta. The conclusions of this investigation may be summarized as follows:-

1. Aortic lesions, found in every rabbit given vitamin D, are accepted as evidence of the toxicity of the doses given.

2. Of the heart lesions caused by vitamin D, lesions immediately subjacent to the endocardium apparently occur most frequently, focal lesions of the myocardium less frequently and coronary artery lesions least frequently.

3. Vitamin D_2 is at least as toxic to the heart as vitamin D_3, and may be more so.

4. It was not found possible to assess the prognosis of these heart lesions, and their ultimate effect, if any, on heart function, but myocardial and coronary artery lesions such as these could account for the electrocardiographic changes in idiopathic hypercalcaemia.

5. Myocardial and coronary artery lesions are unlikely to be caused by the usual prophylactic doses of vitamin D unless the vitamin were to exert a cumulative effect by such a mechanism as has been postulated in idiopathic hypercalcaemia of infancy.

6./

6.   Detailed histological examination of the heart of infants dying in the course of idiopathic hypercalcaemia is an important requirement.

Electrocardiograms of 3 newborn infants suffering from hypocalcaemia were studied, and the following conclusions were reached:-

1.   A prolonged ST segment is a reliable index of hypocalcaemia, but accurate measurement of the ST segment is not always possible.

2.   The QTc value decreases when the serum calcium has returned to normal.

3.   Detection of an unduly high QTc value due to mild hypocalcaemia in the early neonatal period is impossible until more information concerning normal values at this age is available.

4.   There is no evidence to suggest that a tall T wave is a sign of hypocalcaemia.

Electrocardiograms of 3 children suffering from hyperkalaemia were studied, and the following conclusions were reached:-

1.   The presence of hyperkalaemia is suggested by tall pointed T waves following relatively small R waves, but this is not invariable.

2.   The electrocardiogram does not accurately reflect high levels of serum potassium.

Electrocardiograms/

Electrocardiograms of 4 children suffering from hypokalaemia were studied, and the following conclusions were reached:-

1. The differentiation between hypokalaemic and hypocalcaemic changes in the ST-T complex may present difficulty.

2. The presence of hypokalaemia is suggested by a long low wave in the vicinity of the T wave, with apparent lengthening of the QT interval (QTc). This wave is composed of the T wave closely followed by a prominent U wave, and the true QT interval (QTc) is not lengthened.

3. These signs are not closely related to the level of serum potassium, but the electrocardiogram may nevertheless provide valuable information during the treatment of children suffering from potassium depletion perhaps because the electrocardiographic signs are more closely dependent upon the total body potassium.

Electrocardiograms of 3 infants suffering from hypernatraemia were studied, and the following conclusions were reached:-

1. Hypernatraemia is not apparently accompanied by a uniform pattern of electrocardiographic abnormality.

2. Hypernatraemia does not potentiate the effect of hypokalaemia on the electrocardiogram.

Electrocardiography in Idiopathic Hypercalcaemia and Other
Cation Disorders of Childhood

APPENDICES

APPENDIX I

Technique employed for the recording and

reading of electrocardiograms

All electrocardiograms were recorded by the author to ensure
as far as possible the maintenance of standard conditions.

The recording was made with the subject in the recumbent
position, and in most of the healthy infants between one and two
hours after a feed had been taken.   In no instance was a sedative
given beforehand, or any drug known to affect the conducting
mechanism of the heart.

A six-channel photographic electrocardiograph (Elema-
'Klinik') was used and standardized before each examination so
that a current of one millivolt produced a beam deflection of
one centimetre.   The three standard limb leads were recorded
simultaneously.   On the recording paper the distance between
thick vertical lines represents 0.1 second, and between thick
horizontal lines, 1 millivolt.

Close attention was given to the contour of wave formations.
Measurements were made of the cardiac cycle (R-R' interval), the
P wave, PR (PQ) interval, QRS complex, T wave and QT interval,
and expressed to the nearest 0.01 second.   Whenever there was
variation in the length of the cardiac cycle within an individual
record, an average value, expressed to the nearest 0.005 second, was
calculated after measurement of as many cycle lengths as were
available;   from this figure the average heart rate was obtained.
The measurement of the PR interval was made in standard lead II
from the beginning of the P wave to the onset of the Q wave.

Measurement/

Measurement of the T wave sometimes presented difficulty especially in the separation of its ascending limb from the ST segment. The T wave was held to commence at the point where the even course of the ST segment was interrupted by a distinct change in direction or angulation. This determination was facilitated by comparing the synchronously recorded leads. Difficulty in separating a closely adjacent U wave from the T wave was not experienced, except in the presence of hypokalaemia.

Whenever there was difficulty in determining the length of the P wave, QRS complex or T wave this was resolved by comparing the interval in each of the synchronously recorded leads. The measurement was taken from the lead in which the length was greatest. Slight variation in the length of the QT interval was occasionally encountered, and in such cases an average value was calculated.

The measured QT interval was corrected to compensate for the influence of heart rate by the application of a modification of Bazett's formula (1920), the term QTc being used in preference to K to denote the resulting value:

$$QTc = \frac{QT \; (seconds)}{\sqrt{cardiac \; cycle \; (seconds)}}$$

This calculation was made by slide-rule.

The length of the ST segment was calculated by subtracting the sum of the QRS complex and the T wave, measured in the lead in which they were longest, from the average QT interval. Thus the shortest ST segment was obtained for study, and this is in accordance with the recommendation of Ashman and Hull (1945).

APPENDIX II

Scope of statistical calculations

based on data obtained from the

electrocardiograms of healthy infants and

of patients suffering from idiopathic

hypercalcaemia of infancy.

Electrocardiography of healthy infants

The material for analysis consisted of electrocardiograms
of 100 infants, 25 infants in each quarter of the first year
of life. The mean value, the standard deviation of the mean
and the range of the following measurements were calculated
for each 3 month period and for the entire 12 month period:-
the heart rate, the length of the P wave, PR (PQ) interval,
QRS complex, T wave, QT interval, ST segment and the value of
QTc. The mean age of the entire sample and the standard
deviation of this mean were calculated.

A frequency distribution table was constructed to relate
heart rate to age. Frequency distribution tables were
constructed to relate the length of the P wave, PR interval,
QRS complex, T wave, QT interval and ST segment both to age
and to heart rate. Coefficients of correlation (r) were
established from these by the product-moment method and the
coefficients examined for significance. Equations were
evolved representing the linear regression of the various
electrocardiographic measurements on both age (weeks) and
heart rate (beats per minute).

Electrocardiography in idiopathic hypercalcaemia

Coefficients of correlation (r) were established to
relate/

relate the value of QTc, the length of the ST segment and the length of the T wave in 53 electrocardiograms from 24 patients with idiopathic hypercalcaemia to the level of serum calcium. The significance of these coefficients was determined. Equations representing the linear regression of the QTc value, ST length and T length on serum calcium were formulated.

Forty-six electrocardiograms obtained from 21 patients examined during the first year of life were divided into two groups of 23 electrocardiograms. This division was made to separate electrocardiograms with changes in the contour of the ST-T complex from those without changes in contour. Mean values, and the standard deviation of the means, were determined for the age at the time of examination, the heart rate, the length of the P wave, PR interval, QRS complex, T wave, ST segment, QT interval and for the QTc value. The data concerning the P wave, PR interval, QRS complex, T wave, ST segment, QT interval and QTc value obtained from these two groups of electrocardiograms and from the electrocardiograms of healthy infants were subjected to analyses of variance and the significance of differences between means determined.

APPENDIX III

Electrocardiographic data obtained from

healthy infants

Electrocardiographic Data from Healthy Infants

First Quarter   2 Weeks to 3 Months

Age (wks.)	Rate (per min.)	P Wave (secs.)	PR Interval (secs.)	QRS Complex (secs.)	T Wave (secs.)	QT Interval (secs.)	QTc	ST Segment (secs.)	Cycle Length (secs.)
3	136	0.06	0.09	0.05	0.12	0.26	0.39	0.09	0.44
3	162	0.05	0.12	0.05	0.11	0.24	0.395	0.08	0.37
2	207	0.06	0.10	0.05	0.10	0.21	0.39	0.06	0.29
3	132	0.06	0.09	0.05	0.11	0.26	0.385	0.10	0.455
3	133	0.04	0.09	0.06	0.12	0.26	0.39	0.08	0.45
3	135	0.05	0.10	0.06	0.12	0.25	0.38	0.07	0.445
3	166	0.06	0.09	0.05	0.14	0.25	0.415	0.06	0.36
7	158	0.06	0.09	0.05	0.13	0.25	0.405	0.07	0.38
4	135	0.04	0.09	0.05	0.11	0.27	0.405	0.11	0.445
7	154	0.06	0.11	0.06	0.12	0.25	0.40	0.07	0.39
6	182	0.06	0.10	0.06	0.11	0.23	0.40	0.06	0.33
7	118	0.05	0.09	0.05	0.12	0.28	0.39	0.11	0.51
7	193	0.06	0.09	0.05	0.09	0.23	0.415	0.09	0.31
9	188	0.06	0.09	0.05	0.10	0.22	0.39	0.07	0.32
8	140	0.07	0.14	0.06	0.11	0.27	0.41	0.10	0.43
9	167	0.06	0.09	0.06	0.09	0.24	0.40	0.09	0.36
12	140	0.06	0.10	0.06	0.12	0.27	0.41	0.09	0.43
10	140	0.06	0.08	0.07	0.12	0.27	0.41	0.08	0.43
11	130	0.07	0.12	0.07	0.13	0.28	0.415	0.08	0.46
11	140	0.06	0.09	0.06	0.10	0.26	0.395	0.10	0.43
10	130	0.06	0.10	0.07	0.09	0.25	0.37	0.09	0.46
11	176	0.06	0.10	0.05	0.10	0.23	0.395	0.08	0.34
10	176	0.06	0.10	0.06	0.12	0.24	0.41	0.06	0.34
7	182	0.06	0.10	0.06	0.09	0.23	0.40	0.07	0.33
7	171	0.06	0.11	0.06	0.11	0.24	0.405	0.07	0.35

Electrocardiographic Data from Healthy Infants

Second Quarter   3 to 6 Months

Age (wks.)	Rate (per min.)	P Wave (secs.)	PR Interval (secs.)	QRS Complex (secs.)	T Wave (secs.)	QT Interval (secs.)	QTc	ST Segment (secs.)	Cycle Length (secs.)
15	143	0.07	0.12	0.06	0.12	0.24	0.37	0.06	0.42
14	129	0.06	0.10	0.06	0.11	0.26	0.385	0.09	0.46
13	136	0.07	0.12	0.06	0.12	0.26	0.39	0.08	0.44
14	200	0.06	0.09	0.05	0.10	0.21	0.385	0.06	0.30
14	162	0.07	0.09	0.06	0.10	0.24	0.395	0.08	0.37
18	150	0.07	0.12	0.07	0.10	0.25	0.395	0.08	0.40
22	122	0.08	0.13	0.06	0.13	0.28	0.40	0.09	0.49
20	176	0.06	0.09	0.06	0.10	0.24	0.41	0.08	0.34
17	136	0.06	0.09	0.06	0.11	0.25	0.38	0.08	0.44
17	128	0.06	0,10	0.05	0.10	0.25	0.365	0.10	0.47
21	154	0.06	0.09	0.06	0.12	0.24	0.385	0.06	0.39
18	126	0.07	0.09	0.06	0.15	0.27	0.39	0.06	0.475
21	167	0.06	0.10	0.06	0.12	0.24	0.40	0.06	0.36
21	126	0.06	0.10	0.06	0.12	0.26	0.40	0.08	0.475
21	125	0.08	0.10	0.06	0.12	0.26	0.375	0.08	0.48
22	128	0.06	0.10	0.07	0.12	0.26	0.38	0.07	0.47
23	167	0.07	0.10	0.05	0.11	0.24	0.40	0.08	0.36
22	141	0.07	0.10	0.07	0.10	0.25	0.385	0.08	0.425
25	128	0.07	0.10	0.06	0.12	0.26	0.38	0.08	0.47
20	146	0.07	0.10	0.05	0.11	0.25	0.39	0.09	0.41
18	128	0.06	0.10	0.06	0.10	0.26	0.38	0.10	0.47
16	118	0.06	0.11	0.06	0.14	0.27	0.38	0.07	0.51
14	162	0.06	0.10	0.05	0.12	0.24	0.395	0.07	0.37
18	*135	0.06	0.08	0.06	0.12	0.26	0.39	0.08	0.445
14	146	0.08	0.12	0.06	0.12	0.26	0.405	0.08	0.41

* Denotes data from subject obtained at second electrocardiographic examination.

Electrocardiographic Data from Healthy Infants

Third Quarter   6 to 9 Months

Age (wks.)	Rate (per min.)	P Wave (secs.)	PR Interval (secs.)	QRS Complex (secs.)	T Wave (secs.)	QT Interval (secs.)	QTc	ST Segment (secs.)	Cycle Length (secs.)
27	182	0.06	0.10	0.06	0.11	0.22	0.385	0.05	0.33
27	136	0.07	0.14	0.07	0.12	0.25	0.38	0.06	0.44
28	122	0.06	0.12	0.06	0.15	0.29	0.415	0.08	0.49
28	133	0.06	0.09	0.06	0.13	0.26	0.39	0.07	0.45
29	140	0.06	0.12	0.06	0.11	0.26	0.395	0.09	0.43
28	133	0.08	0.13	0.06	0.13	0.26	0.39	0.07	0.45
28	120	0.07	0.11	0.07	0.12	0.26	0.37	0.07	0.50
29	122	0.07	0.11	0.06	0.12	0.26	0.37	0.08	0.49
30	133	0.07	0.11	0.07	0.12	0.26	0.39	0.07	0.45
31	118	0.07	0.12	0.07	0.13	0.28	0.39	0.08	0.51
35	115	0.07	0.11	0.07	0.12	0.26	0.36	0.07	0.52
30	133	0.06	0.12	0.05	0.12	0.26	0.39	0.09	0.45
31	125	0.06	0.09	0.05	0.13	0.28	0.405	0.10	0.48
35	128	0.07	0.14	0.07	0.13	0.26	0.38	0.06	0.47
27	128	0.06	0.09	0.07	0.14	0.28	0.41	0.07	0.47
31	120	0.06	0.10	0.07	0.15	0.29	0.41	0.07	0.50
27	140	0.07	0.11	0.07	0.13	0.26	0.395	0.06	0.43
28	125	0.07	0.10	0.06	0.13	0.28	0.405	0.09	0.48
27	128	0.07	0.12	0.07	0.11	0.26	0.38	0.08	0.47
27	133	0.07	0.12	0.07	0.14	0.27	0.405	0.06	0.45
30	138	0.07	0.11	0.06	0.12	0.25	0.38	0.07	0.435
27	128	0.07	0.10	0.06	0.12	0.25	0.365	0.07	0.47
27	*133	0.07	0.10	0.07	0.11	0.26	0.39	0.08	0.45
27	*129	0.06	0.11	0.06	0.12	0.28	0.415	0.10	0.46
27	*120	0.06	0.10	0.06	0.13	0.27	0.38	0.08	0.50

* Denotes data obtained from subject at second electrocardiographic examination.

Electrocardiographic Data from Healthy Infants

Fourth Quarter   9 to 12 Months

Age (wks.)	Rate (per min.)	P Wave (secs.)	PR Interval (secs.)	QRS Complex (secs.)	T Wave (secs.)	QT Interval (secs.)	QTc	ST Segment (secs.)	Cycle Length (secs.)
40	102	0.06	0.10	0.07	0.14	0.29	0.38	0.08	0.59
40	140	0.08	0.11	0.06	0.11	0.25	0.38	0.08	0.43
40	133	0.06	0.08	0.07	0.13	0.27	0.40	0.07	0.45
43	140	0.08	0.13	0.06	0.11	0.25	0.38	0.08	0.43
43	150	0.06	0.11	0.06	0.12	0.25	0.395	0.07	0.40
48	150	0.08	0.10	0.07	0.12	0.26	0.41	0.07	0.40
46	136	0.07	0.11	0.07	0.13	0.26	0.39	0.06	0.44
47	113	0.07	0.11	0.06	0.14	0.28	0.385	0.08	0.53
52	150	0.08	0.11	0.06	0.14	0.26	0.41	0.06	0.40
51	133	0.06	0.09	0.07	0.14	0.28	0.42	0.07	0.45
47	176	0.06	0.09	0.06	0.11	0.23	0.395	0.06	0.34
40	148	0.07	0.13	0.06	0.12	0.25	0.395	0.07	0.405
48	143	0.07	0.10	0.06	0.13	0.25	0.385	0.06	0.42
39	118	0.07	0.12	0.07	0.15	0.29	0.405	0.07	0.51
41	128	0.06	0.10	0.07	0.13	0.26	0.38	0.06	0.47
40	140	0.07	0.12	0.07	0.13	0.26	0.395	0.06	0.43
45	*110	0.06	0.10	0.08	0.15	0.28	0.38	0.05	0.545
42	*120	0.06	0.09	0.06	0.14	0.28	0.395	0.08	0.50
44	*200	0.07	0.08	0.06	0.11	0.23	0.42	0.06	0.30
40	*103	0.06	0.10	0.07	0.15	0.29	0.38	0.07	0.58
40	*133	0.06	0.08	0.07	0.11	0.25	0.375	0.07	0.45
48	130	0.08	0.11	0.07	0.12	0.26	0.385	0.07	0.46
48	154	0.08	0.11	0.07	0.12	0.26	0.415	0.07	0.39
48	130	0.08	0.13	0.07	0.12	0.26	0.385	0.07	0.46
40	*109	0.07	0.12	0.08	0.15	0.29	0.39	0.06	0.55

* Denotes data obtained from subject at second electrocardiographic examination.

Data from Two Electrocardiographic Examinations of Ten Subjects

Age (wks.)	Rate (per min.)	P Wave (secs.)	PR Interval (secs.)	QRS Complex (secs.)	T Wave (secs.)	QT Interval (secs.)	QTc	ST Segment (secs.)	Cycle Length Average (secs.)	Minimum (secs.)	Maximum (secs.)
I 6	171	0.06	0.09	0.06	0.10	0.24	0.405	0.08	0.35	0.34	0.36
II 18	135	0.06	0.08	0.06	0.12	0.26	0.39	0.08	0.445	0.44	0.45
I 11	154	0.06	0.09	0.05	0.12	0.26	0.415	0.09	0.39	0.39	0.39
II 27	129	0.06	0.11	0.06	0.12	0.28	0.415	0.10	0.46	0.46	0.46
I 11	150	0.06	0.10	0.05	0.13	0.26	0.41	0.08	0.40	0.40	0.40
II 27	120	0.06	0.10	0.06	0.13	0.27	0.38	0.08	0.50	0.50	0.50
I 13	154	0.07	0.11	0.06	0.12	0.24	0.37	0.06	0.39	0.39	0.39
II 27	133	0.07	0.10	0.07	0.11	0.26	0.39	0.08	0.45	0.43	0.46
I 22	135	0.06	0.09	0.07	0.12	0.27	0.405	0.08	0.445	0.43	0.46
II 40	103	0.06	0.10	0.07	0.15	0.29	0.38	0.07	0.58	0.54	0.63
I 22	113	0.06	0.10	0.07	0.13	0.28	0.385	0.08	0.53	0.52	0.54
II 40	133	0.06	0.08	0.07	0.11	0.25	0.375	0.07	0.45	0.42	0.48
I 27	128	0.07	0.14	0.07	0.13	0.27	0.395	0.07	0.47	0.45	0.49
II 40	109	0.07	0.12	0.08	0.15	0.29	0.39	0.06	0.55	0.55	0.55
I 32	122	0.06	0.12	0.06	0.14	0.28	0.40	0.08	0.49	0.48	0.50
II 42	120	0.06	0.09	0.06	0.14	0.28	0.395	0.08	0.50	0.47	0.54
I 34	115	0.06	0.12	0.07	0.13	0.28	0.39	0.08	0.52	0.50	0.54
II 45	110	0.06	0.10	0.08	0.15	0.28	0.38	0.05	0.545	0.50	0.61
I 34	182	0.06	0.09	0.06	0.12	0.24	0.42	0.06	0.33	0.32	0.34
II 44	200	0.07	0.08	0.06	0.11	0.23	0.42	0.06	0.30	0.30	0.30

I and II denote first and second examinations respectively.

APPENDIX IV

Frequency distribution tables,
correlation coefficients and linear regression equations
relating the electrocardiographic intervals
of 100 healthy infants to age and heart rate.

Frequency distribution of 100 observations of heart rate related to age.

HEART RATE PER MINUTE	0-5	6-11	12-17	18-23	24-29	30-35	36-41	42-47	48-53	TOTAL No.
100-109							3			3
110-119		1	1		2	1	2			7
120-129			2	6	10	3	1	1		23
130-139	5	2	2	1	5	3	2	1	3	24
140-149		3	3	2	2		3	1	1	15
150-159		2		2				1	3	8
160-169	2	1	2	2						7
170-179		3		1				1		5
180-189		3			1					4
190-199		1								1
200-209	1		1					1		3
TOTAL No.	8	16	11	14	18	8	10	8	7	100

Column header: AGE IN WEEKS →

Correlation coefficient (r) of heart rate with age = − 0.2921 (P < 0.01).
Linear regression of heart rate (beats per minute) on age (weeks) = − 0.463597 Age + 153.1.
The regression line has been drawn in.

LENGTH OF P WAVE

Frequency distribution of 100 values according to age.

AGE (WEEKS)

	0–5	6–11	12–17	18–23	24–29	30–35	36–41	42–47	48–53	Total
.04	2									2
.05	2	1								3
.06	4	13	7	7	7	3	5	4	1	51
.07		2	3	5	10	5	4	3	1	33
.08			1	2	1		1	1	5	11
Total	8	16	11	14	18	8	10	8	7	100

P WAVE (SECONDS)

Correlation coefficient (r) of P wave with age = + 0.5045 (P < 0.01)

LENGTH OF P WAVE

Frequency distribution of 100 values according to heart rate.

HEART RATE PER MINUTE

	100/9	110/9	120/9	130/9	140/9	150/9	160/9	170/9	180/9	190/9	200/9	
.04	0	0	0	2	0	0	0	0	0	0	0	2
.05	0	1	0	1	0	0	1	0	0	0	0	3
.06	2	2	13	10	4	4	4	5	4	1	2	51
.07	1	4	8	8	8	1	2	0	0	0	1	33
.08	0	0	2	3	3	3	0	0	0	0	0	11
	3	7	23	24	15	8	7	5	4	1	3	100

P WAVE (SECONDS)

Correlation coefficient (r) of P wave with heart rate = $- 0.1003$ (not significant)

Linear regression of P on age and heart rate:

$$P = + 0.000297851 \text{ Age} + 0.0000185905 \text{ Heart rate} + 0.054914.$$

LENGTH OF PR INTERVAL

Frequency distribution of 100 values according to age.

AGE (WEEKS)

PR INTERVAL (SECONDS)	0-5	6-11	12-17	18-23	24-29	30-35	36-41	42-47	48-53	
.08		1		1			2	1		5
.09	5	6	3	3	2	1		2	1	23
.10	2	5	4	8	6	1	3	1	2	32
.11		2	1		4	3	1	3	3	17
.12	1	1	3	1	4	2	3			15
.13				1	1		1	1	1	5
.14		1			1	1				3
	8	16	11	14	18	8	10	8	7	100

Correlation coefficient (r) of PR interval with age = + 0.2034 (P<0.05)

LENGTH OF PR INTERVAL

Frequency distribution of 100 values according to heart rate.

HEART RATE PER MINUTE

	100/9	110/9	120/9	130/9	140/9	150/9	160/9	170/9	180/9	190/9	200/9	
.08	0	0	0	3	1	0	0	0	0	0	1	5
.09	0	1	4	7	1	2	3	2	1	1	1	23
.10	2	1	12	3	4	1	3	2	3	0	1	32
.11	0	3	3	4	2	4	0	1	0	0	0	17
.12	1	2	2	4	4	1	1	0	0	0	0	15
.13	0	0	1	2	2	0	0	0	0	0	0	5
.14	0	0	1	1	1	0	0	0	0	0	0	3
	3	7	23	24	15	8	7	5	4	1	3	100

PR INTERVAL (SECONDS)

Correlation coefficient (r) of PR interval with heart rate = $- 0.2302$ ($P < 0.05$)

Linear regression of PR on age and heart rate:

PR = 0.000148316 Age – 0.000117216 Heart rate + 0.117111.

LENGTH OF QRS COMPLEX

Frequency distribution of 100 values according to age.

AGE (WEEKS)

QRS COMPLEX (SECONDS)	0-5	6-11	12-17	18-23	24-29	30-35	36-41	42-47	48-53	
.05	6	5	3	2		2				18
.06	2	8	8	9	11	1	2	6	2	49
.07		3		3	7	5	7	1	5	31
.08							1	1		2
	8	16	11	14	18	8	10	8	7	100

Correlation coefficient (r) of QRS complex on age = + 0.5287 (P<0.01).

LENGTH OF QRS COMPLEX

Frequency distribution of 100 values according to heart rate.

HEART RATE PER MINUTE

QRS COMPLEX (SECONDS)	100/9	110/9	120/9	130/9	140/9	150/9	160/9	170/9	180/9	190/9	200/9	
.05		1	2	4	1	1	4	1	1	1	2	18
.06		2	14	8	10	4	3	4	3		1	49
.07	2	3	7	12	4	3						31
.08	1	1										2
	3	7	23	24	15	8	7	5	4	1	3	100

Correlation coefficient (r) of QRS complex on heart rate = − 0.4351 (P<0.01)

Linear regression of QRS on age and heart rate:

$$QRS = 0.000229693 \text{ Age} - 0.000101189 \text{ Heart rate} + 0.070458.$$

LENGTH OF T WAVE

Frequency distribution of 100 values according to age.

AGE (WEEKS)

T WAVE (SECONDS)	0-5	6-11	12-17	18-23	24-29	30-35	36-41	42-47	48-53	
.09		4								4
.10	1	3	3	4						11
.11	3	3	2	2	4		2	3		19
.12	3	4	5	6	6	4	1	1	4	34
.13		2		1	5	3	3	1	1	16
.14	1		1		2		1	2	2	9
.15				1	1	1	3	1		7
	8	16	11	14	18	8	10	8	7	100

Correlation coefficient (r) of T wave with age $= + 0.3288$ $(P < 0.01)$.

LENGTH OF T WAVE

Frequency distribution of 100 values according to heart rate

HEART RATE PER MINUTE

T WAVE (SECONDS)	100/9	110/9	120/9	130/9	140/9	150/9	160/9	170/9	180/9	190/9	200/9	
.09				1			1		1	1		4
.10			2		2	1	1	2	1		2	11
.11			2	5	5		2	2	2		1	19
.12		2	8	11	5	5	2	1				34
.13		1	6	5	3	1						16
.14	1	2	2	2		1	1					9
.15	2	2	3									7
	3	7	23	24	15	8	7	5	4	1	3	100

Correlation coefficient (r) of T wave with heart rate $= -0.7124$ $(P < 0.01)$

Linear regression of T on age and heart rate:

$$T = 0.000137207 \text{ Age} - 0.000441859 \text{ Heart rate} + 0.180616.$$

LENGTH OF QT INTERVAL

Frequency distribution of 100 values according to age.

AGE (WEEKS)

QT INTERVAL (SECONDS)	0–5	6–11	12–17	18–23	24–29	30–35	36–41	42–47	48–53	
.21	1		1							2
.22		1			1					2
.23		4						2		6
.24	1	3	3	4						11
.25	2	3	2	3	2	1	3	2	1	19
.26	3	1	3	5	9	4	2	1	5	33
.27	1	2	2	1	2		1			9
.28		2		1	3	2		3	1	12
.29					1	1	4			6
	8	16	11	14	18	8	10	8	7	100

Correlation coefficient (r) of QT interval on age = + 0.3275 (P<0.01).

LENGTH OF QT INTERVAL

Frequency distribution of 100 values according to heart rate.

HEART RATE PER MINUTE

	100/9	110/9	120/9	130/9	140/9	150/9	160/9	170/9	180/9	190/9	200/9	
.21											2	2
.22									2			2
.23								2	2	1	1	6
.24					1	1	6	3				11
.25			2	6	6	4	1					19
.26		1	11	13	5	3						33
.27		1	2	3	3							9
.28		4	6	2								12
.29	3	1	2									6
	3	7	23	24	15	8	7	5	4	1	3	100

QT INTERVAL (SECONDS)

Correlation coefficient (r) of QT interval on heart rate = -0.8572 ($P < 0.01$).

Linear regression of QT on age and heart rate:

$$QT = 0.000104393 \text{ Age} - 0.000649885 \text{ Heart rate} + 0.347013.$$

LENGTH OF ST SEGMENT

Frequency distribution of 100 values according to age.

AGE (WEEKS)

ST INTERVAL (SECONDS)	0-5	6-11	12-17	18-23	24-29	30-35	36-41	42-47	48-53	
.05					1			1		2
.06	2	2	2	3	3	1	3	3	2	21
.07	1	5	2	1	5	4	5	1	5	29
.08	2	3	4	7	6	1	2	3		28
.09	1	3	2	2	2	1				11
.10	1	2	1	1	1	1				7
.11	1	1								2
	8	16	11	14	18	8	10	8	7	100

Correlation coefficient (r) of ST segment with age $= -0.3554$ ($P < 0.01$).

LENGTH OF ST SEGMENT

Frequency distribution of 100 values according to heart rate.

HEART RATE PER MINUTE

ST SEGMENT (SECONDS)	100/9	110/9	120/9	130/9	140/9	150/9	160/9	170/9	180/9	190/9	200/9	
.05		1							1			2
.06	1		3	3	4	2	2	2	1		3	21
.07	1	3	5	10	1	5	1	1	2			29
.08	1	2	8	6	5	1	3	2				28
.09			3	3	3		1			1		11
.10			4	1	2							7
.11		1		1								2
	3	7	23	24	15	8	7	5	4	1	3	100

Correlation coefficient (r) of ST segment with heart rate = – 0.2583 (P≑0.01).

Linear regression of ST on age and heart rate:

$$ST = -0.000432765 \text{ Age} - 0.00022920 \text{ Heart rate} + 0.1184.$$

APPENDIX V

Electrocardiographic data and serum

calcium levels of patients with

idiopathic hypercalcaemia.

Case No.	Age (weeks)	Rate (/min.)	P (secs.)	PR (secs.)	QRS (secs.)	T (secs.)	QT (secs.)	QTc	ST (secs.)	Serum Calcium (mg./100 ml.)
2	29	113	0.08	0.14	0.07	0.20	0.29	0.40	0.02	16.5
	30	122	0.07	0.13	0.08	0.16	0.26	0.37	0.02	18.6
4	33	158	0.07	0.10	0.06	0.15	0.24	0.39	0.03	15.3
	34	120	0.06	0.14	0.06	0.15	0.28	0.40	0.07	13.5
	35	115	0.07	0.14	0.06	0.21	0.30	0.415	0.03	11.4
5	35	133	0.06	0.12	0.05	0.16	0.24	0.36	0.03	17.6
	35	133	0.06	0.14	0.06	0.20	0.26	0.39	0.00	18.0
	36	130	0.06	0.14	0.06	0.18	0.26	0.38	0.02	15.1
	36	125	0.07	0.14	0.05	0.16	0.28	0.405	0.07	11.3
6	48	136	0.06	0.10	0.05	0.13	0.24	0.36	0.06	11.8
11	21	127	0.06	0.11	0.04	0.16	0.28	0.41	0.08	10.1
	33	127	0.07	0.12	0.05	0.15	0.28	0.41	0.08	11.2
13	35	118	0.06	0.12	0.06	0.14	0.30	0.42	0.10	11.0
	37	120	0.06	0.15	0.06	0.15	0.28	0.40	0.07	10.5
16	36	139	0.08	0.13	0.07	0.18	0.26	0.40	0.01	16.2
	37	128	0.07	0.13	0.07	0.18	0.28	0.41	0.03	11.0
	38	120	0.07	0.13	0.07	0.18	0.29	0.41	0.04	12.6
18	33	130	0.07	0.13	0.06	0.16	0.25	0.37	0.03	13.1
19	36	154	0.06	0.10	0.07	0.16	0.27	0.43	0.04	14.6
20	26	150	0.06	0.10	0.06	0.14	0.25	0.395	0.05	13.4
21	43	143	0.07	0.11	0.05	0.12	0.23	0.355	0.06	12.1
	46	136	0.07	0.12	0.05	0.12	0.24	0.36	0.07	10.9
23	35	150	0.07	0.14	0.06	0.13	0.24	0.38	0.05	12.3

Data from 23 electrocardiograms with changes in contour of ST-T complex obtained from infants with idiopathic hypercalcaemia, related to age and serum calcium level.

Case No.	Age (weeks)	Rate (/min.)	P (secs.)	PR (secs.)	QRS (secs.)	T (secs.)	QT (secs.)	QTc	ST (secs.)	Serum Calcium (mg./100 ml.)
1	32	130	0.07	0.12	0.06	0.16	0.26	0.38	0.04	12.8
2	31	122	0.07	0.12	0.06	0.13	0.25	0.36	0.06	9.0
5	37	145	0.06	0.10	0.06	0.14	0.25	0.385	0.05	11.3
	39	143	0.06	0.11	0.05	0.13	0.24	0.37	0.06	10.9
7	38	115	0.06	0.10	0.05	0.17	0.29	0.40	0.07	10.3
8	20	166	0.06	0.11	0.04	0.12	0.23	0.38	0.07	13.9
	21	154	0.07	0.12	0.04	0.13	0.24	0.38	0.07	12.8
10	37	115	0.07	0.12	0.07	0.13	0.25	0.35	0.05	12.8
	44	115	0.07	0.12	0.07	0.12	0.26	0.36	0.07	12.7
11	36	115	0.07	0.12	0.05	0.14	0.28	0.39	0.09	10.96
12	4	125	0.06	0.10	0.06	0.14	0.26	0.375	0.06	11.6
13	52	150	0.06	0.10	0.06	0.12	0.24	0.38	0.06	8.3
14	20	125	0.06	0.11	0.06	0.13	0.26	0.375	0.07	11.8
15	14	158	0.06	0.09	0.04	0.10	0.23	0.37	0.09	12.5
16	39	196	0.06	0.10	0.07	0.10	0.21	0.375	0.04	12.6
	40	115	0.07	0.12	0.07	0.14	0.29	0.40	0.08	10.3
	41	146	0.07	0.10	0.07	0.14	0.28	0.435	0.07	10.4
	42	120	0.07	0.12	0.07	0.15	0.28	0.40	0.06	12.3
18	34	158	0.06	0.11	0.05	0.12	0.23	0.37	0.06	11.8
19	38	143	0.07	0.11	0.06	0.14	0.27	0.415	0.07	11.7
20	29	171	0.06	0.09	0.05	0.17	0.25	0.42	0.03	14.5
22	4	162	0.06	0.09	0.06	0.13	0.24	0.395	0.05	11.1
24	34	120	0.06	0.13	0.06	0.13	0.26	0.37	0.07	10.4

Data concerning 23 electrocardiograms without changes in contour of ST-T complex obtained from infants with idiopathic hypercalcaemia, related to age and serum calcium level.

Idiopathic hypercalcaemia

Additional electrocardiographic data used for correlation with serum calcium from children aged over 1 year at time of examination.

Case No.	QTc	ST (secs.)	T (secs.)	Serum Calcium (mg./100 ml.)
3	0.42	0.06	0.15	10.2
9	0.425	0.08	0.16	15.3
	0.385	0.07	0.12	14.9
	0.37	0.06	0.12	14.8
17	0.45	0.08	0.16	14.2
	0.40	0.04	0.19	10.4
	0.43	0.07	0.12	12.2

APPENDIX VI

Correlation of QTc value, length of ST segment and T wave with serum calcium of patients suffering from idiopathic hypercalcaemia.

QTc VALUE

Frequency distribution of 53 values related to serum calcium.

QTc	SERUM CALCIUM (mg/100ml.)											
	8	9	10	11	12	13	14	15	16	17	18	
·35					2							2
·36		1	1	1	1					1		5
·37			2	3	2	1	1			1		10
·38	1			1	3	1	1	1				8
·39			1	1		1		1			1	5
·40			4	1	1	1			2			9
·41			1	4	1							6
·42			1	1			1	1				4
·43			1		1		1					3
·44												0
·45							1					1
	1	1	11	12	11	4	5	3	2	1	2	53

Correlation coefficient (r) of QTc with serum calcium = + 0.015 (not significant).
Linear regression of QTc on serum calcium (mg./100 ml.) = 0.00015340 x serum calcium + 0.3881389.
The regression line has been drawn in.

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LENGTH OF ST INTERVAL

Frequency distribution of 53 values related to serum calcium.

SERUM CALCIUM (mg/100ml)

ST INTERVAL (seconds)	8	9	10	11	12	13	14	15	16	17	18	
0										1	1	1
·01									1			1
·02							1	1		1		3
·03				2		1	1	1		1		6
·04			1		3		1					5
·05				2	2	1						5
·06	1	1	2	3	2		1					10
·07			5	3	3	2	1					14
·08			2	1				1	1			5
·09			1		1							2
·10				1								1
	1	1	11	12	11	4	5	3	2	1	2	53

Correlation coefficient (r) of ST with serum calcium = − 0.5924 (P < 0.01).
Linear regression of ST (seconds) on serum calcium (mg./100 ml.) = − 0.00577118 x serum calcium + 0.125856.
The regression line has been drawn in.

T WAVE

Frequency distribution of 53 values related to serum calcium.

SERUM CALCIUM (mg/100 ml)

T WAVE (seconds)	8	9	10	11	12	13	14	15	16	17	18	
·10					2							2
·11												O
·12	1		1	1	3	1	2					9
·13		1	2	3	3							9
·14			3	4		1						8
·15			2	1	1	1		1				6
·16			1	1	1	1	2	1		1	1	9
·17			1				1					2
·18				1	1			1	1			4
·19			1									1
·20									1		1	2
·21				1								1
	1	1	11	12	11	4	5	3	2	1	2	53

Correlation coefficient (r) of T with serum calcium = + 0.3700 (P < 0.01).
Linear regression of T (seconds) on serum calcium (mg./100 ml.) = 0.00412869 x serum calcium + 0.096514.
The regression line has been drawn in.

APPENDIX VII

Analyses of variance of time intervals

in electrocardiograms of healthy subjects and of

patients with idiopathic hypercalcaemia

according to the presence or absence of changes

in the contour of the ST-T complex.

Length of P wave

	Number in group	Arithmetic mean	Standard Deviation
Healthy infants Control group	100	0.06480	0.0081
Idiopathic hypercalcaemia Normal ST-T	23	0.06430	0.0051
Idiopathic hypercalcaemia Abnormal ST-T	23	0.06652	0.0065

Analysis of variance: No significant difference
between the means (F = 0.6). A comparison of the
control group against the normal ST-T group or of
the control group against the abnormal ST-T group
would require a difference of 0.0034 to be
significantly different from zero. A comparison
of the normal ST-T group against the abnormal ST-T
group would require a difference of 0.044 to be
significantly different from zero.

Length of PR interval

	Number in group	Arithmetic mean	Standard Deviation
Healthy infants Control group	100	0.1041	0.0141
Idiopathic hypercalcaemia Normal ST-T	23	0.1091	0.0106
Idiopathic hypercalcaemia Abnormal ST-T	23	0.1252	0.0167

Analysis of variance: Significant difference between means ($F > 20$: $P < 0.01$). The standard error of the difference of the means of the control and normal ST-T groups or of control and abnormal ST-T groups is 0.00325 and a difference of 0.0064 is therefore significant at 5% level of significance. Clearly the abnormal ST-T group is causing the significant differences. The standard error of the difference between the means of the normal ST-T and abnormal ST-T groups is 0.00415 and a difference of 0.0082 is therefore significant.

Length of QRS complex

	Number in group	Arithmetic mean	Standard Deviation
Healthy infants Control group	100	0.0617	0.0074
Idiopathic hypercalcaemia Normal ST-T	23	0.0578	0.0098
Idiopathic hypercalcaemia Abnormal ST-T	23	0.0596	0.0093

Analysis of variance: No significant difference between the means $(F = 2.40)$. The standard error of the difference between the means of the control and normal ST-T groups or of the control and abnormal ST-T groups is 0.001885. The standard error of the difference between the means of the normal ST-T and abnormal ST-T groups is 0.002403.

Length of T wave

	Number in group	Arithmetic mean	Standard Deviation
Healthy infants Control group	100	0.1202	0.0147
Idiopathic hypercalcaemia Normal ST–T	23	0.1339	0.01777
Idiopathic hypercalcaemia Abnormal ST–T	23	0.1596	0.02486

Analysis of variance: Significant difference between means $(F => 40 : P < 0.01)$. The standard error of the difference between the means of the control and normal ST–T groups or of the control and abnormal ST–T groups is 0.003958. The standard error of the difference between the means of the normal ST–T and abnormal ST–T groups is 0.005046. Each mean therefore differs significantly from any other.

Length of QT interval

	Number in group	Arithmetic mean	Standard Deviation
Healthy infants Control group	100	0.2574	0.01750
Idiopathic hypercalcaemia Normal ST-T	23	0.2544	0.0208
Idiopathic hypercalcaemia Abnormal ST-T	23	0.2652	0.0213

Analysis of variance: No significant difference between the means ($F = 2.205$). The standard error of the difference between the means of the control and normal ST-T groups or of the control and abnormal ST-T groups is 0.004318. The standard error of the difference between the means of the normal ST-T and abnormal ST-T groups is 0.005506.

Value of QTc

	Number in group	Arithmetic mean	Standard Deviation
Healthy infants Control group	100	0.3926	0.01433
Idiopathic hypercalcaemia Normal ST-T	23	0.3852	0.02129
Idiopathic hypercalcaemia Abnormal ST-T	23	0.3926	0.02136

Analysis of variance: No significant difference between the means (F = 1.87). The standard error of the difference between the means of the control and normal ST-T groups or of the control and abnormal ST-T groups is 0.003886. The standard error of the difference between the means of the normal ST-T and abnormal ST-T groups is 0.004954.

Length of ST segment

	Number in group	Arithmetic mean	Standard Deviation
Healthy infants Control group	100	0.0754	0.01298
Idiopathic hypercalcaemia Normal ST-T	23	0.0626	0.01484
Idiopathic hypercalcaemia Abnormal ST-T	23	0.0461	0.02589

Analysis of variance: Significant difference between means $(F => 30 : P < 0.01)$. The standard error of the difference between the means of the control and normal ST-T groups or of the control and abnormal ST-T groups is 0.003685. The standard error of the difference between the means of the normal ST-T and abnormal ST-T groups is 0.004698.

APPENDIX VIII

Standard limb lead electrocardiograms
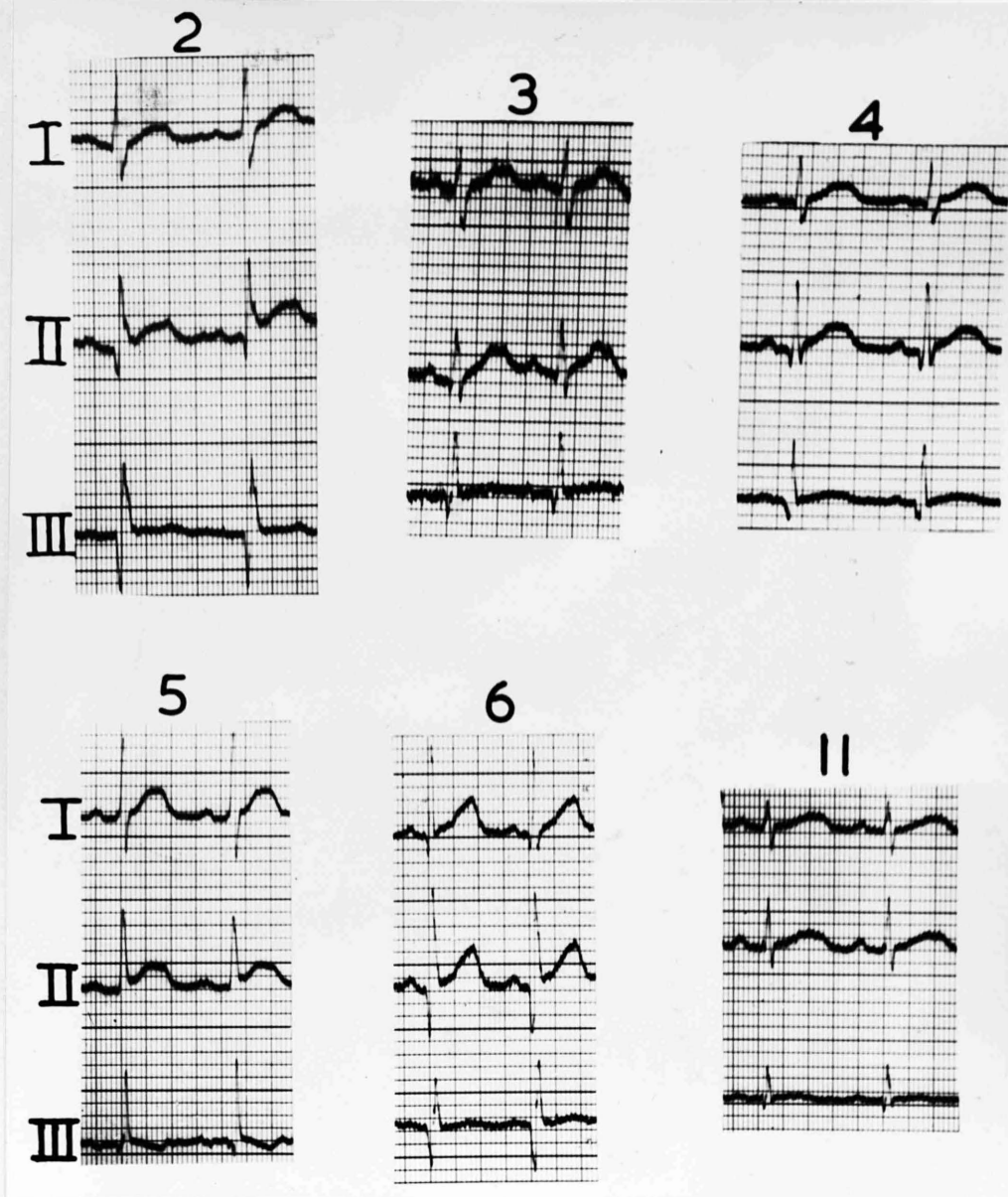
from patients with idiopathic hypercalcaemia.

Standard limb leads from one electrocardiogram of patients
showing abnormal contour of ST-T complex.

Case No.	Serum Calcium (mg./100 ml.)
2	16.5
3	10.2
4	13.5
5	17.6
6	11.8
11	11.2
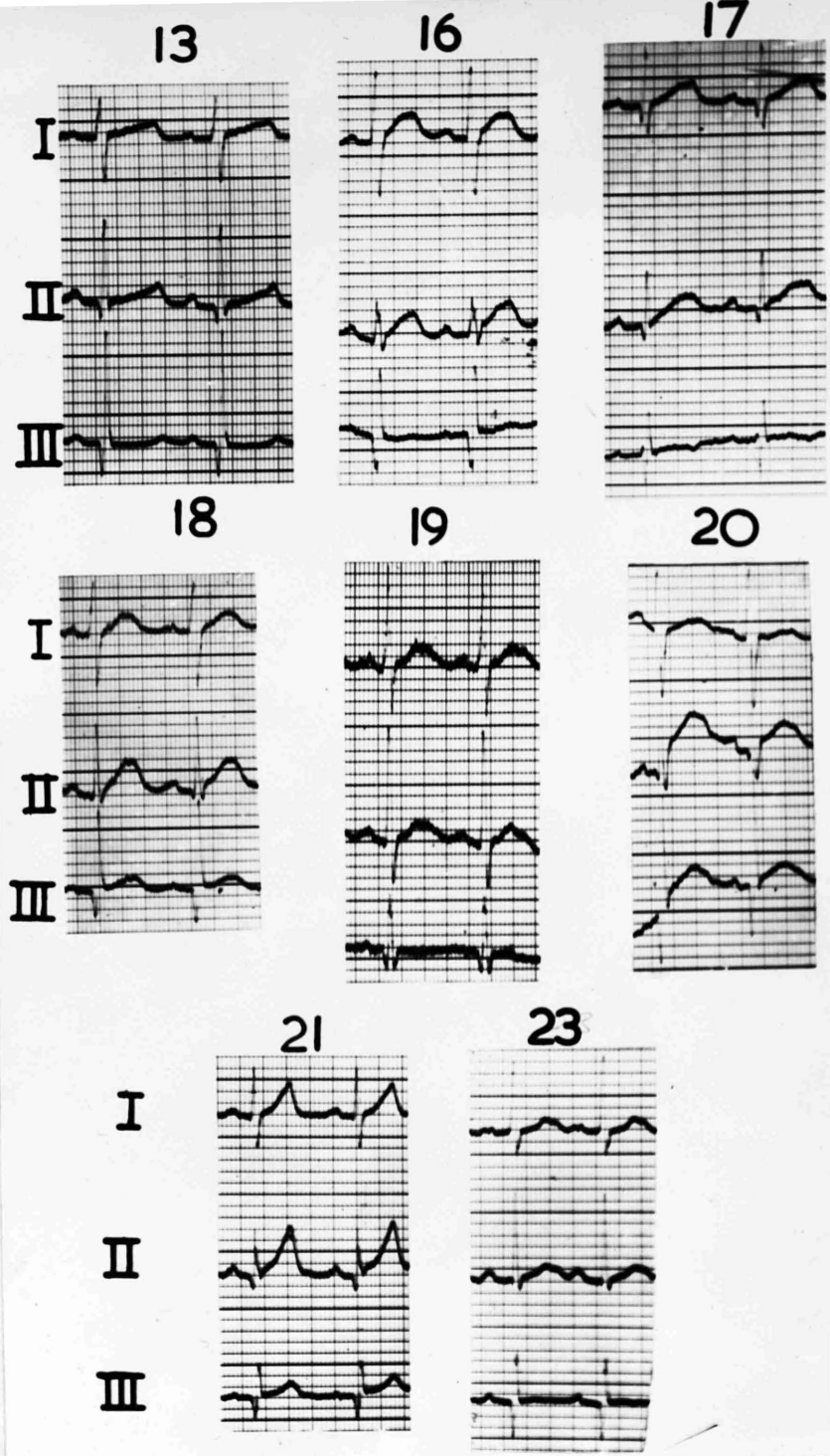
Standard limb leads from one electrocardiogram of patients showing abnormal contour of S-T-T complex.

Case No.	Serum Calcium (mg./100 ml.)		Case No.	Serum Calcium (mg./100 ml.)
13	11.0		19	14.6
16	16.2		20	13.4
17	10.4		21	12.1
18	13.1		23	12.3
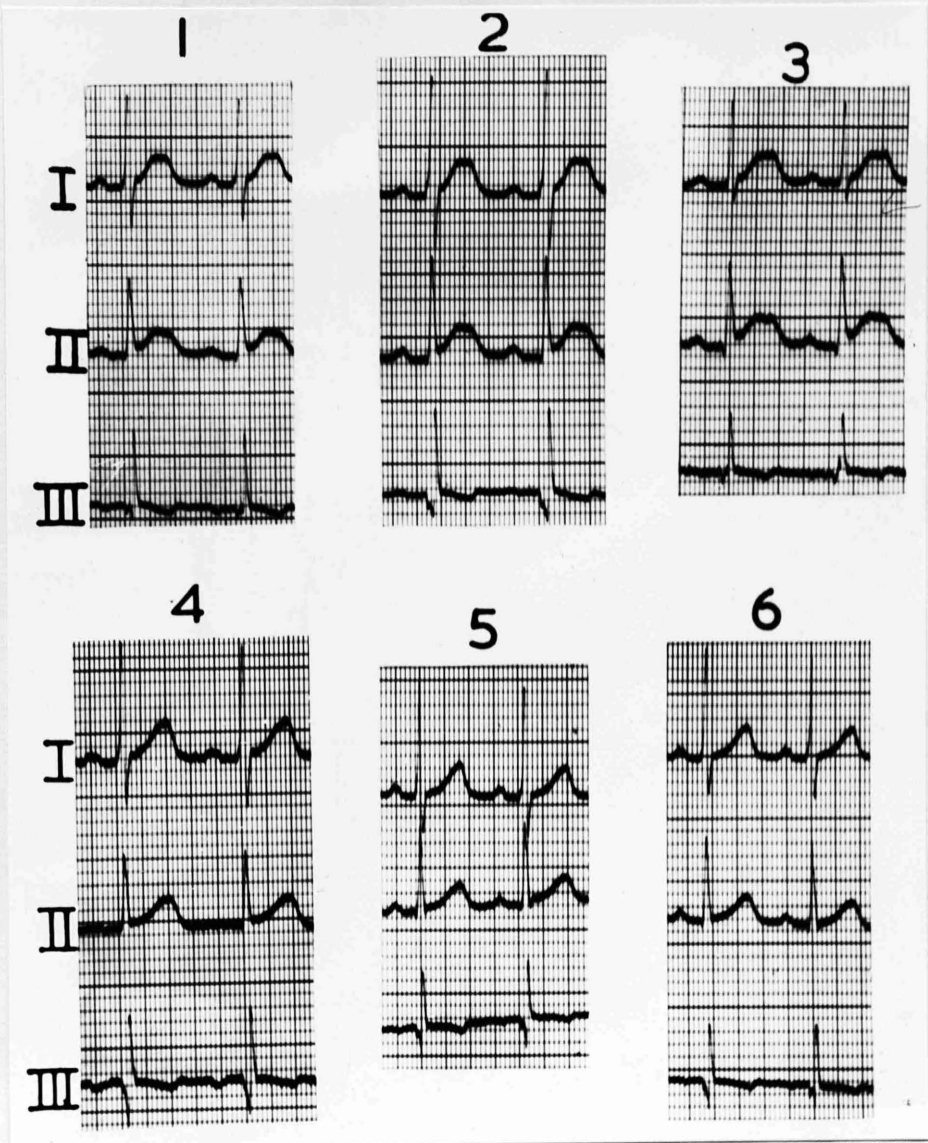
Standard limb lead electrocardiograms obtained at weekly intervals from a patient with idiopathic hypercalcaemia (Case No. 5). The abnormal contour of the ST-T complex in leads I and II gradually disappears.

E.C.G.	Serum Calcium (mg./100 ml.)
1	17.6
2	18.0
3	15.1
4	11.3
5	11.3
6	10.9
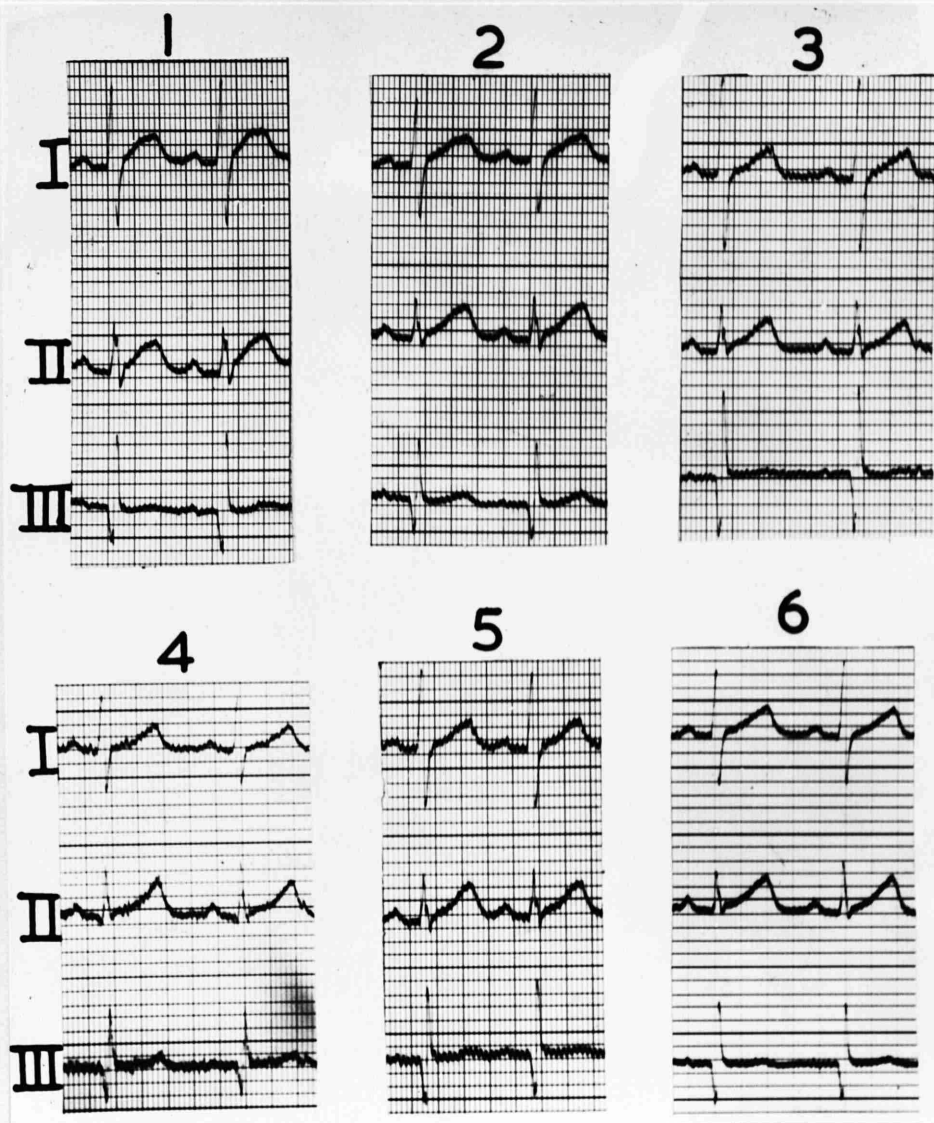
Standard limb lead electrocardiograms obtained at weekly intervals from a patient with idiopathic hypercalcaemia (Case No. 16). The abnormal contour of the ST-T complex in leads I and II gradually disappears.

E.C.G.	Serum Calcium (mg./100 ml.)
1	16.2
2	11.0
3	12.6
4	12.6
5	10.3
6	10.4

chemical determination, quoted in these text

with the separation of

Nitrogen Clarke

DETERMINATION

Water

Residue dry sample

enzyme

cholesterol

APPENDIX IX

Biochemical methods.

The chemical determinations quoted in these investigations were made in the department of biochemistry at the Royal Hospital for Sick Children where the following methods were in use.

DETERMINATION	METHOD
Serum calcium	Kramer B. and Tisdall F. (1921) J. Biol. Chem. 47. 475.
Serum potassium and sodium	Flame photometry.
Serum phosphorus	Briggs A. P. (1922) J. Biol. Chem. 53. 13.
Serum cholesterol	Zlatkis A., Zak B. and Boyle A. J. (1953) J. Lab. Clin. Med. 41. 486.
Plasma total CO_2	Van Slyke D.D. and Cullen G.E. (1917) J. Biol. Chem. 30. 290.
Plasma chloride	Schales O., and Schales S. S. (1941) J. Biol. Chem. 140. 879.
Blood sugar	Folin O. and Wu H. (1920) J. Biol. Chem. 41. 367. (modified for application to capillary blood)
Blood non-protein nitrogen	Folin O. and Svedberg A. (1930) J. Biol. Chem. 88. 85.

APPENDIX X

Diet given to rabbits during

vitamin D feeding experiment.

After weaning, treated and control rabbits received the following diet together with a daily allocation of greens.

Constituents of diet:	Percentage composition
Bran	15
Dried grass meal	30
Ground nut cake	15
Linseed cake	10
Dried meat & bone meal	8
Barley meal	20
Sodium chloride	1
Calcium carbonate	1

Analysis of diet:	Approximate percentage composition
Protein	21.7
Fat	6.6
Carbohydrate	40.5
Fibre	11.5
Moisture	11.5
Ash	8.6

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Cation Disorders of Childhood

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relation to The Biochemical Background.   Those which follow
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