

T H E S I S

Presented for the Degree of PH.D.,

EDINBURGH UNIVERSITY,

on

ACUTE CALCIUM DEFICIENCY in relation to DISEASE

in FARM ANIMALS, with

SPECIAL REFERENCE to MILK FEVER in COWS.

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July, 1929

Degree conferred 26th Oct. 1929.



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INTRODUCTORY.

The following thesis had its origin in an investigation into the nature of milk fever in cows, which the author commenced in 1924 in conjunction with Dr Henry Dryerre, Lecturer in Bio-Physics, Edinburgh University.

The causation of milk fever presented a problem in etiology, round which, for the last hundred years, much speculative controversy has centred, and we planned to promulgate a reasoned working hypothesis upon the nature of the disease which could be later subjected to experimental investigation.

The hypothesis was published in the Veterinary Record in 1925, and the results of subsequent investigations, designed to test its accuracy, were presented to the Dumfries and Galloway Veterinary Medical Association in September, 1928.

Such part of that research as was performed by the author has been included in the work to be described; while a considerable portion of the paper of 1928 for which the author was responsible has been freely used in the preparation of the present text.

The/

The results of an investigation into lambing sickness have already been published as a separate paper, a copy of which is herein included.

A SHORT ACCOUNT OF MILK FEVER
IN COWS.

Milk fever was recognised as a clinical entity only as late as the end of the eighteenth century. The first record seems to be that of ⁽¹⁾EBERHARDT who noted its occurrence in 1793.

In England JOHN PRICE referred to the disease in "The New useful Farrier and Complete Cow. Leech" (1806), and in the following year, SKELLETT, another English Veterinarian gave a good description in a work entitled "A Practical Treatise on the Parturition of the Cow".

In French veterinary literature the disease seems to have received recognition only as late as 1837 when FAVRE described it in his "Vétérinaire Campagnard".

These facts suggest that Milk fever appeared in such incidence as to warrant its record only in comparatively recent times; had it existed earlier it is difficult to believe that a disease of such economic importance could have failed to attract attention/

attention, for its peculiar time relation to parturition and its acute characteristic course render its diagnosis, even by unskilled agriculturists, a matter of comparative ease.

It is significant that the appearance of the disease corresponds with the commencement of the intensive development of the cow as a producer of milk, and this is further suggested by the fact that in countries in which milk fever was unknown, the introduction of breeding stock possessing deep milking qualities was followed by the appearance of the disease in their progeny.

Milk fever usually occurs within thirty hours after calving, and the parturition is almost invariably easy and uncomplicated; cows are occasionally attacked during the last few days of pregnancy, but never before the commencement of lactation. The onset is sudden and characterised by excitement and convulsive spastic seizures of variable duration and intensity; these, in turn are succeeded by some degree of coma. In a proportion of cases the earlier convulsive phase is so slight that it escapes notice, and the animal quickly lapses into a condition of somnolence which progressively deepens into a partial or completely comatose state. The pulse is at first accelerated and full but later becomes/

becomes soft and almost imperceptible.

Throughout the whole course of the attack which is afebrile in character, there is a diminution in intestinal peristalsis approaching complete cessation, and the milk secretion is also markedly diminished.

Fatal cases run a course of about two or three days, but in those which terminate favourably, the recovery is usually rapid and complete. In a large proportion of cases the attack may be said to be without prodrome or convalescence. After the initial attack the disease tends to recur at each subsequent parturition.

Milk fever increased in the frequency of its occurrence until it came to be regarded as among the most common diseases incidental to parturition; and since the disease proved highly resistant to treatment, and usually attacked those cows which were the deepest milkers, it became one of the greatest scourges of the dairying industry.

In 1897, J.J. SCHMIDT, a Danish veterinary practitioner, in the belief that the disease represented an intoxication of mammary origin, discovered a specific remedy in the injection of the mammary gland with a solution of iodide of potassium. This treatment was subsequently modified since it was found/

found that results were equally satisfactory when the mammae were distended with sterile water; and the modern treatment which consists in mammary insufflation with filtered air has proved of such specific curative value that the mortality of from fifty to sixty per cent. has been reduced to less than one per cent.

But mammary inflation, while it furnished us with a specific means of cure, rendered the problem of the pathogenesis of milk fever the more intriguing, since we remained in complete ignorance both of the nature of the disease and of the action of the remedial treatment, and as was to be expected a large number of speculative hypotheses have been from time to time enunciated.

THEORIES UPON THE NATURE OF MILK FEVER.

Apart from its scientific interest, a short discussion of the various theories upon the nature of the disease, which during the last hundred years have been from time to time advanced may serve to illustrate the extraordinary diversity of view to which this mysterious malady has given rise in the minds/

minds of Veterinarians throughout Europe and America.

Although many of the theories cannot stand examination in the light of modern physiological knowledge, they attracted wide attention at the time of their publication. Nor must they be regarded as worthless for it was because of their study and the elimination of false hypotheses that we have been gradually led to an understanding of the essential nature of the disease.

The theories may be conveniently grouped as follows:-

(1) GENERAL INFLAMMATION.

In Britain the early authorities believed the disease to be of an inflammatory nature and this theory may be regarded as the first to be generally accepted thus. CLATER (The Cattle Doctor 1825) states that the cause is:-"An inflammatory state of the udder which is frequently induced by the animal taking cold, and from a redundancy of blood in the system. About the second or third day after calving a much greater quantity of blood than usual is determined to the udder for the secretion of milk, but when the udder is inflamed this act does not take place, and the blood is in consequence transferred to some other/

other parts as the peritoneum, the bowels, kidneys etc. which deranges the whole animal frame and produces milk fever".

DELABERE ⁽²⁾ BLAINE believed it to be a general inflammatory condition resulting from arrestment of the milk secretion.

⁽³⁾ YOUATT states that the disease is primarily an inflammation of the womb or of the peritoneum but "soon assumes a general inflammatory state as rapid in its progress as it is violent in its nature and speedily followed by a prostration of vital power that often bids defiance to every stimulus".

⁽⁴⁾ HARRISON and ⁽⁵⁾ HERING also regarded it as an inflammatory fever.

(2) DERANGEMENTS OF THE NERVOUS SYSTEM.

⁽⁶⁾ CONTAMINE believed that at the time of calving there existed an accumulation of "nervous energy" which was utilised during the act of parturition. If the calving were very easy the "nervous influx" was diverted to the brain and cord and in some unexplained manner produced inflammation of these structures.

⁽⁷⁾ FRIEND regarded milk fever as an inflammation/

inflammation of the medulla: ROBINSON⁽⁸⁾ as a
cerebritis; RALPH⁽⁹⁾ as encephalitis.

According to KÜHNE⁽¹⁰⁾ the disease represented a primary paralysis of the ganglionic cells of the sympathetic nervous system which extended eventually to the spinal cord and to the brain.

Similar theories have been advanced by RYCHNER⁽¹¹⁾
STEWART⁽¹²⁾ BINZ⁽¹³⁾ FUSCH⁽¹⁴⁾ ROLL⁽¹⁶⁾
BAUMEISTER-RUEFF⁽¹⁷⁾ and others.

GÜNTHER and FÉLIZET⁽¹⁸⁾ saw the initiation of the malady in the mental perturbation which may follow the removal of the calf from the dam.

(3) GENERAL CIRCULATORY DISTURBANCES.

Numerous authorities including BREDO,⁽⁸⁷⁾
POMAYER,⁽⁸⁸⁾ KREUTZER,⁽⁸⁹⁾ and SEITTER⁽⁹⁰⁾ have ascribed the disease to a fall in blood pressure following the crisis of parturition.

SEITTER claimed that artificial distension of the udder caused a pronounced rise in the general blood pressure and he explained the action of mammary inflation as a curative in this way. His work however has, been carefully repeated by AUGER⁽⁹¹⁾ who, finds that mammary distension has practically no influence upon the blood pressure. (see page 29)

(4). CEREBRAL ANAEMIA.

FRANCK in 1871 ⁽¹⁹⁾ was the originator of the theory of cerebral anaemia.

FRANCK'S ideas were based upon the views of ROSENBERG & TRAUBE, in their study of the cause of eclampsia in women. He supposed that after parturition the contracting uterus forced back its supply of blood into the general circulation. A sudden hyperaemia resulted in the tissues and an exudation of lymph occurred from the cerebral blood vessels - this exudate by pressure on the vessels caused their obliteration and so produced cerebral anaemia.

This notion was altogether too fantastic; but the idea that the disease was a cerebral anaemia received wide acceptance and the theory under various modifications has found favour with numerous observers down to the present day.

GLASS ⁽²⁰⁾ suggested that during the later stages of pregnancy, the gravid uterus produced an excessive pressure upon the abdominal and thoracic organs. After the birth of the calf this compression was suddenly removed, and thereupon an influx of blood occurred into the abdominal and thoracic vessels; the congestion of these viscera brought about
a/

a consequent withdrawal of blood from the brain and resulted in a cerebral anaemia.

Similar hypotheses were advanced on the continent by HAUBNER⁽²¹⁾, WERMER⁽²²⁾, and PREHR⁽²³⁾. ARONSOHN⁽²⁴⁾, BARONI⁽²⁵⁾, ZOPPINI⁽²⁶⁾ and DOMMERHOLD⁽²⁷⁾, believed that cerebral anaemia resulted in consequence of the congestion which occurs in the mammae at the commencement of milk secretion.

M'CONNELL⁽²⁸⁾ attributed the supposed cerebral anaemia to a constriction of the cerebral vessels which followed upon a condition of 'shock', produced by the sudden emptying of the udder by hand. Similar theories were enunciated by ZEHL and others.

BILLINGS⁽²⁹⁾ supposed that an exaggerated excitability of the nervous mechanism of the uterus provoked in a reflex way, a spasm of the small arteries of the brain and kidneys, and as a result anaemia of these organs occurred.

HESS⁽³⁰⁾ believed that bacterial toxins generated in the uterus, produced vaso-motor disturbance, which resulted in cerebral anaemia.

MEIER⁽³¹⁾ in support of the cerebral anaemia theory, claimed to have demonstrated a resemblance between the symptoms of milk fever and those which occur in a cow suffering from severe internal haemorrhages. /

haemorrhages.

(32)
 SONNENBERG believed that a cerebral anaemia in milk fever resulted from a disturbance of the vaso-motor centres; and argued that the factor responsible for this disturbance was contained in the milk, a certain quantity of which, he believed, was reabsorbed into the blood in milk fever. His theory had its origin in the previous observation of SOLT & RIGA, who had claimed to demonstrate the haemostatic properties of milk absorbed from the rectum. In support of this theory SONNENBERG injected rabbits with milk and produced symptoms which he believed to be due to cerebral anaemia. DELMER and others combated SONNENBERG'S conclusions, and pointed out that the symptoms produced in the rabbits were not comparable with those of milk fever. It is now permissible to believe that SONNENBERG'S rabbits actually suffered from a condition of "Anaphylactic Shock".

(33)
 GRATIA & VAN DEN EECKHOUT sought to put the cerebral anaemia theory to the test by means of an acute experiment; -

Using a heifer, the carotid arteries were exposed and clip forceps applied, so that no blood could pass through them. In this way the brain was temporarily/

temporarily deprived of its main blood supply, yet no serious symptoms developed; and throughout the experiment, which extended over nearly two hours, the animal continued to feed.

(5). CEREBRAL CONGESTION.

(34)
VIOLET thought that the disease represented a cerebral congestion. According to his theory, the birth had been too rapidly and too easily effected. The heart, no longer called upon to meet the claims of the foetal circulation, functioned more powerfully than was necessary, so that the blood was driven with greater force upon the Central Nervous System. Vascular ruptures and consequent haemorrhage were the possible result.

(35)
BARLOW held that the disturbance in the sympathetic nervous system led to arrest of secretion and general congestion, especially of the brain and spinal cord. The acceptance of this idea, as offering the most satisfactory explanation of the cause was strongly advocated by Professor WILLIAM WILLIAMS.

(36)
SANSON accepted this idea, but explained the hypothetical cerebral congestion, as FRANCK explained the equally hypothetical cerebral anaemia, by assuming that the contracting uterus forced a large volume of blood into the general circulation. Similar/
ar/

Similar theories were put forward by COX⁽³⁷⁾, BARRON⁽³⁸⁾
and STEWART⁽³⁹⁾.

NOQUET⁽⁴⁰⁾ declared the disease to be due to a congestion of the Cerebro-Spinal System and Splanchnic nerves, resulting from blood plethora, repletion of the stomach at the moment of parturition, and intensity of "the fever of lactation".

CAMPBELL⁽⁴¹⁾ believed the congestion due to the maternal anxiety and distress following the removal of the calf.

AYRAULT⁽⁴²⁾ was of opinion that a cerebral-spinal congestion was determined by "chill," acting directly on the uterus from which the blood was consequently expelled.

TRASBOT⁽⁴³⁾ held that the disease resulted from "chill", which provoked constriction of the superficial blood vessels and so diverted the blood to the spinal cord, which now became congested.

WALLEY⁽⁴⁴⁾ and DENEUBOURG⁽⁴⁵⁾ were among other authorities who postulated a cerebral congestion as the cause.

(6). APOPLEXY.

(46)
 THACKER claimed to have demonstrated the cause in
 Spinal Apoplexy. FESTAL (47), BRAGNARD (48); (49)
 DEVLESHOUER (50), WHINCOP (51) and HESS (52) claimed to
 have found cerebral apoplexy on autopsy.

(53)
 GERRARD stated that in seventy five
 per cent of cases lesions of apoplexy could be dis-
 covered.

(44)
 WALLEY sought to establish a relation-
 ship between Milk Fever and the peculiar disposition
 of the cerebral blood vessels which obtains in bovi-
 dae - the so-called rete mirabile which he believed
 should predispose the cow to cerebral congestion.
 He suggested that the constipation which is so mark-
 ed a feature of the disease, could be regarded as a
 contributory cause, in so far that apoplexy might
 follow upon the animal's straining to pass faeces.

(54)
 BEART SIMONDS reached the definite
 conclusion that the disease represented an apoplec-
 tic condition of the brain and spinal cord and insist-
 ed upon the correctness of the name "Parturient Apo-
 plexy". He referred it to - "some peculiar impres-

"sion exerted upon the uterine nerves at the
 "time of parturition; the disturbance being
 "communicated to the central nerves and from
 "thence/

"thence to the brain; a vast volume of blood not
 "used by the flaccid uterus being at the same
 "time thrown back upon the system and acting as
 "a predisposing cause".

(55)
 WARD suggested that after calving, the cerebral vessels received an excessive supply of blood, for the purpose of meeting the demands occasioned by the natural emotional excitement which the cow exhibits upon first receiving her calf.

If the calf be removed immediately after birth, this emotional instinct is dulled and, after several parturitions, becomes lost, so that although the physiological cerebral influx is still active its psychological utilisation is no longer effected, with resultant cerebral congestion and apoplexy.

This ingenious, if somewhat quixotic hypothesis attempted to explain the curious immunity to milk fever exhibited by primiperae and second calvers, a problem which many more plausible hypotheses left unconsidered.

(7). THROMBOSIS.

(56)
 LAYMAN believed that Milk Fever arose from phlebitis and consequent thrombosis which terminated in embolism.

COX/

(57) COX and (58) WILD also enunciated theories which declared thrombosis to be the cause.

(8). FAT EMBOLISM.

(59) PENBERTHY suggested that the malady arose from embolism of the cerebral blood vessels by fat globules absorbed from the milk. These theories fell in face of the rapid and complete recoveries which follow mammary inflation.

(9). SPINAL TRAUMATISM.

(60) ROGERSON suggested that Milk Fever resulted from spinal traumatism, which was indirectly occasioned by parturition.

"The progress of gestation is very gradual,
 "and consequently produces no effect upon the
 "spine, for, as the foetus enlarges and the womb
 "elongates and expands, so does the spine adapt
 "itself to its burden. But the expulsion of the
 "foetus is so sudden, that the spine returns to
 "its original state and situation too rapidly,
 "after having rid itself of its weight. The
 "spinal marrow in some measure becomes injured
 "sufficiently to produce paralysis".

(10). AERAEMIA.

Upon observing the presence of gas in the cerebral vessels in cows which had died from Milk Fever, CARSTEN HARMS⁽⁶¹⁾ deduced that this aeraemia was the cause of the disease and resulted from the introduction of air into the uterine blood vessels which had ruptured during the act of calving.

(11). THEORIES OF INFECTION.
GENERAL INFECTION.

Following upon the researches of PASTEUR and the discovery that many diseases of unknown origin were due to the presence of pathogenic micro-organisms it was natural that numerous theories which sought to attribute the disease to microbial invasion should be enunciated - thus following ALLEMANI⁽⁶²⁾ and HARRISON-THOMAS⁽⁶³⁾ who suggested that⁽⁶⁴⁾ the disease was a septicaemia, POTIEZ and CONREUR discovered in the blood a streptococcus which they considered to be the cause of the disease. This micro-organism, while pathogenic to laboratory animals, failed, however, to reproduce the disease when injected into cows.

VAN/

VAN DER VELDE⁽⁶⁵⁾ attributed the disease to the presence of a streptococcus associated with the colon bacillus in the blood.

(12). BACTERIAL INFECTION OF UTERINE ORIGIN.

In 1878 RAINAUD⁽⁶⁶⁾ had postulated a toxæmia due to absorption by the blood of toxins generated in decomposition of the lochia. Similar hypotheses were advanced by PAVESSE,⁽⁶⁷⁾ WANNONIUS,⁽⁶⁸⁾ LAFOSSÉ,⁽⁶⁹⁾ STOCKLETH,⁽⁷⁰⁾ LANZILLOTI-BUONSANTI,⁽⁷¹⁾ ZUNDEL,⁽⁷²⁾ and LYMAN⁽¹⁵⁾.

The hypothesis was elaborated by SCHMIDT-MULHEIM⁽⁷³⁾ who recognised in the symptoms of milk fever a resemblance to those of botulism. The theory was later adopted by FRIEDBERGER⁽⁷⁴⁾ and FRÖHNER in Germany but received little support.

This idea, however, has recently been reintroduced again by PUGH (1925)⁽⁷⁵⁾ who suggests that the disease results from the absorption of botulism - like toxins to which the animal is predisposed by the presence of a ketosis.

NOCARD,⁽⁷⁶⁾ after declaring his belief that the disease was infectious, discovered a pyogenic organism in the uterine mucous membrane and held that this organism played an important part in the production of the disease.

GUILLEBEAU,⁽⁷⁷⁾ HESS,⁽³⁰⁾ TRINCHERA,⁽⁷⁸⁾ COZETTE,⁽⁷⁹⁾ LIGNIÈRES⁽⁸⁰⁾ and others have all incriminated various micro-organisms/

micro-organisms found in the uterus in the production of the disease.

(81)
HARTENSTEIN attributed the disease to absorption of certain products elaborated in the muscular layer of the uterus, and especially to uric acid formed during the act of parturition.

(13). INFECTION OF MAMMARY ORIGIN.

The theory of intoxication due to toxins elaborated by micro-organisms in the mammae has had numerous partisans. It was THOMASSEN (82) who first suggested that milk fever was due to organisms which developed in the colostrum and variants of this idea have been set forth by KNUSEL, (83) HEBBELYNCK, (84) (85) PARKER and DELMER. (86)

After the discovery of the curative effects of mammary inflation, it was believed by many that the causal organism in the mammae must be anaerobic and that the presence of air prevented its further growth.

(14). ANAPHYLAXIS.

The attractive theory of Anaphylaxis as the cause of milk fever was first advanced by MAREK (92) and/

and later developed by VAN GOIDSENHOVEN⁽⁹³⁾ but all attempts to reproduce the disease by injections of placental emulsion of milk and of colostrum have failed.

(15). AVITAMINOSIS.

As is well known the discovery of vitamins led to the further discovery that lack of these substances produced certain conditions which are referred to as "deficiency diseases".

It was believed by BAYARD⁽⁹⁴⁾ that milk fever represented such a condition, but no deficiency disease is known, the onset of which is so sudden as that of milk fever or which gives such immediate response to treatment.

(16). AUTOINTOXICATION.

The conception of an autointoxication as the cause of milk fever has perhaps received a greater following than any other.

The site of the toxin formation has been variously suggested. FRIEND,⁽⁹⁵⁾ HODGES,⁽⁹⁶⁾ FISCHER,⁽⁹⁷⁾ D. PUGH,⁽⁹⁸⁾ CESARE ALLEMANI,⁽⁹⁹⁾ ABADIE,⁽¹⁰⁰⁾ SCHUTT,⁽¹⁰¹⁾ STEWART⁽³⁹⁾ and KAISER⁽¹⁰²⁾ have all supposed the intestine/

intestine to be the seat of toxin formation. RAINAUD⁽⁶⁶⁾
 has ascribed its origin to the uterus; STOHRER,⁽¹⁰³⁾
⁽¹⁰⁴⁾ WIENERS, ⁽¹⁰⁵⁾ NASH, ⁽¹⁰⁶⁾ THOMPSON, believed that milk
 re-absorbed into the blood represented the toxic
 factor, but it was to Professor GRATIA⁽¹⁰⁷⁾ in 1896
 that we are indebted for the precise hypothesis
 which indicated the mammae as the seat of auto-intox-
 ication.

It is true that GRATIA'S hypothesis has
 since been found to have no foundation in fact but,
 curiously enough it led by a series of false premises
 to the discovery of the specific cure of the disease.

GRATIA believed that when lactation is
 established an enormous number of glandular cells
 are thrown off from the secretory lining membrane of
 the udder, the bulk of this waste cellular material
 escapes in the colostrum but a portion of it is re-
 absorbed by the blood and there constitutes a toxin
 or leucomaine as GRATIA called it; the greater the
 activity of the mammary gland the more massive would
 be the amount of leucomaine absorbed. This theory
 had numerous supporters.

In support of GRATIA'S hypothesis DELMER⁽¹⁰⁸⁾
 injected colostrum from Milk Fever cases into the
 blood of healthy cows and produced symptoms which he
 claimed/

claimed to be those of milk fever; but it was pointed out by VALLEE⁽¹⁰⁹⁾ that the milk of healthy cows could prove toxic even after all micro-organisms had been removed from it by filtration. Actually the condition produced in the experimental cows was similar to that which occurred in SONNENBERG'S rabbits - namely - "Anaphylactic Shock".

The year 1897 marks an epoch in the history of milk fever. In that year SCHMIDT,⁽¹¹⁰⁾ a veterinary practitioner in Kolding, Denmark, inspired by GRATIA'S theory, subjected the milk of affected cows to microscopic examination. He discovered what he believed to be evidence of cellular disintegration and concluded that some ferment or toxin within the udder was responsible for the decomposition of its endothelium.

In point of fact SCHMIDT made a false observation for, what he mistook for degenerated cells were normal colostrum corpuscles, and had he controlled his observations by examining the first milks of healthy cows he would have found the same types of cells.

It was extraordinarily fortunate that he did not do so, for, having satisfied himself that the cause/

cause of the disease existed within the udder as a living virus he immediately set himself to devise a means for its destruction.

The powerful antiseptic action of iodine was well known but it was of too irritant a nature for introduction into the mammae. SCHMIDT'S choice fell upon the iodide of potassium, and he injected a solution of this drug into the udder of his next case of milk fever. Iodide of potassium is of course devoid of any antiseptic action.

His first case made a complete recovery within a few hours.

Other cases responded to the treatment in the same way and SCHMIDT quickly communicated his discovery to his brother practitioners. Their reports were enthusiastic and soon the "Schmidt Treatment" became general with the result that the mortality from the disease fell from 50 or 60% to fifteen per cent. Later, several modifications and improvements in the method were introduced and with the modern method of mammary insufflation the mortality is to-day less than one per cent.

So it came about that upon a false observation, which in turn gave rise to a hastily formed and erroneous conclusion there was discovered

a/

a therapeutic method, the effects of which were as miraculous as its action was inexplicable.

To SCHMIDT'S efforts, ill-founded though they may have been, we must acknowledge a discovery which has enabled Veterinary Science to render almost negative the effects of one of the most serious maladies to which the parturient cow is subject.

But while a specific cure for the disease had been discovered the cause of milk fever remained a mystery. Indeed the very specificity of the cure rendered the nature of the malady all the more obscure, and the problem was the more attractive by reason of its apparent simplicity.

In 1924 Dr Henry Dryerre and I resolved to undertake an investigation of milk fever; up to that time no clue to the nature of the disease had been discovered, and we considered it desirable to attempt
by/

by a process of reasoning to evolve a working hypothesis which could later be put to the test of experiment and so serve as a basis for future research.

Commencing with the fact that specific cure resulted, no matter whether antiseptic fluids, sterile water, oxygen or air were injected into the udder, it seemed obvious that the effect, whatever it might be, resulted from mechanical distension of the mammae.

We then premised that simple distension of the mammae must act either:-

(1) by eliciting some endocrine disturbance,
and/or

(2) by mechanically retarding or arresting milk secretion, and so preventing the loss in the milk of some substance vital to the organism.

That the disease was in some way closely associated with milk secretion was suggested by the facts that:-

- (1) Its appearance as a clinical entity was coincident with the commencement of the development of the modern heavy milking strains.
- (2) It was much more prevalent in dairy breeds as distinct from beef breeds.
- (3) It almost invariably attacked those individuals which specially possessed deep milking qualities.

(4)/

- (4) The period of greatest susceptibility in an individual corresponded to the period of greatest milk secretion.

The following Table quoted by Law (132) is compiled from veterinary records in Denmark and Bavaria, and clearly indicates the age incidence:-

AGE) YRS)	3	4	5	6	7	8	9	10	11	12	13
NO.) of) CAS) -ES)	8	21	65	160	171	202	117	124	44	70	78

Primiparae were very rarely affected.

- (5) The rapid emptying of the udder by hand might precipitate the onset, while the practice of repeatedly removing small quantities of milk, or, alternatively, permitting the calf to suck the cow for the first few days after calving, was recognised as a valuable preventive procedure.

The milk cow, unlike all other mammals has been bred to produce an enormous quantity of milk, indeed her milk secretion may now be regarded as almost pathological.

The colostrum of the cow is rich in calcium and it was considered likely that the onset of a profuse lactation might occasion a rapid reduction in the concentration of the blood calcium. This idea seemed to be supported by our further observation that/

that the spastic seizures which characterise the early stages of milk fever were tetanic in character.

We then believed that the mere mechanical withdrawal of calcium from the blood as the result of the onset of a profuse secretion of milk could not in itself be regarded as the cause of milk fever, because if this were so every heavy milking cow would be subject to the disease.

For that reason we at that date postulated that some other factors, therefore, must act as a predisposing cause, and we suggested that such might be found in parathyroid disfunction.

Our theory, then ⁽¹¹¹⁾, was briefly as follows:-

(17). PARATHYROID DEFICIENCY
(HYPO-CALCAEMIA THEORY).

As is well known the parathyroid glands play an important part in the regulation and maintenance of the level of calcium in the blood, and in the event of their defective functioning there results a fall in blood calcium and the occurrence of tetany. The parathyroid secretion is also credited with bringing about destruction of toxic metabolites.

We reasoned that the symptoms of milk fever/

fever represented a parathyroid insufficiency, and that a parturient cow about to fall a victim to milk fever was really in a condition of latent tetany.

At this period, also, the blood calcium, already deficient in quantity, suffers further loss by reason of the heavy secretion of colostrum (in which calcium is abundant,) and urgent calls are made upon the parathyroids for the replacement and stabilisation of calcium in the tissues.

Hence the parathyroids, unless they be highly active, are unable to cope with the demands made upon them; calcium falls, toxic compounds gather in the blood, and the condition we call milk fever is the result.

The dramatic cure which follows mammary inflation could, we reasoned, be explained by one or both of the following suggestions.

- (a) mammary inflation might give rise to some obscure reflex stimulation of the ductless glands such as the adrenals and so produce disturbances in metabolism.
- (b) mammary inflation, by distending the udder, might arrest all lactation and the consequent loss of calcium from the blood to the milk. The inflation might therefore produce its curative action by arresting calcium loss and this hypothesis therefore would also explain the recognised efficacy of a restricted withdrawal of milk in the prevention of the disease.

If/

If, as we suggested in our first hypothesis (a) as adrenaline be produced in excess, then inflation should cause (1) a rise in blood pressure and (2) an increase in the blood glucose.

(90)
SEITTER, using a Riva-Rocci apparatus, found that inflation of the udder of cows could raise the blood pressure within half an hour by an average of 55 per cent.

(91)
More recently, AUGER, disputed these findings. He, using a method of greater precision, (utilising an exposed carotid artery), concluded that inflation provoked a slight rise, if any, in the blood pressure. The precise action of inflation upon the blood pressure has still to be determined.

As will be discussed later, an increase in blood glucose usually follows inflation; but the rise when it occurs, is only moderate in degree and since the blood glucose in milk fever is already high, it is difficult to believe that such additional glucose can be of other than minor importance.

If our second suggestion (b) as to the effect of inflation on the disease were correct then it followed that the blood calcium in milk fever should be below normal. Analyses of seven samples of blood from seven consecutive cases of milk fever showed an average/

average of 4.8 mgrms. calcium per cent. serum; a marked reduction when compared with the normal, 9 mgrms. to 11 mgrms. per cent.*

Later in 1925 LITTLE and WRIGHT⁽¹¹²⁾, having observed the similarity which exists between the symptoms of milk fever and those which occurred in an animal deprived of its parathyroids, recorded the results obtained in blood calcium determinations on twelve cases of milk fever. They showed that a considerable diminution, (in mild cases 20 per cent. to 30 per cent., and in severe cases up to 60 per cent.) accompanied the onset of the disease, and they also found that the greater calcium reductions accorded with the more severe cases.

These and our own experiments, therefore furnished considerable support to our hypothesis; but at this stage another and important theory attracted attention.

This new conception probably had its genesis/

* These analyses were performed by Dr Dryerre and are not included in the work to be described.

genesis as far back as 1923⁽¹¹³⁾ when a Canadian veterinary surgeon, whose name is not recorded observed that the comatose phase of milk fever bore a striking resemblance to the coma associated with the depletion of blood glucose (hypo-glycaemia) which follows massive injections of insulin. One case of milk fever was cited in which an intravenous injection of glucose brought about recovery.

Support to this theory was supplied by WIDMARK and CARLENS in Sweden⁽¹¹⁴⁾. These workers showed that inflation of the udder in normal animals caused a rise in the sugar content of the blood, which reached its maximum in 1 to 1½ hours after inflation and then very rapidly diminished.

Further support was given by MAGUIRE⁽¹¹⁵⁾, who recorded one case of milk fever in which an intravenous injection of glucose was followed by recovery.

The theory of hypoglycaemia on prima facie examination appeared very attractive, and it seemed to us that the matter could easily be verified or refuted by determinations of the blood sugar content which obtained in the disease.

In seven cases of milk fever we found the figure for blood sugar to be high (.081 per cent.*).
This/

* These analyses were performed by Dr Dryerre.

This was in accordance with the published findings of other observers, notably HAYDEN and SHOLL⁽¹¹⁶⁾, HAYDEN⁽¹¹⁷⁾ and FISH⁽¹¹⁸⁾, LITTLE and KEITH⁽¹¹⁹⁾, MOUSSU⁽¹²⁰⁾, all of whom have shown that a hyperglycaemia and not a hypoglycaemia was almost invariably present.

WIDMARK and CARLENS (ibid.), although themselves exponents of the hypoglycaemia theory, found that hypoglycaemia existed in the mild cases they examined, but in their severe cases the blood sugar was considerably above normal.

MAGUIRE⁽¹¹⁵⁾ had five cases examined, and found hypoglycaemia occurred in all, but the figure which he took as his standard for normal was considerably above that of other observers.

In short, it may be said that although the blood-sugar figure in milk fever is occasionally low, in the great majority of cases it is increased in amount, and in a considerable number of instances it is remarkably high.

Now, it is possible that an excess of sugar in the blood may be associated with a lack of sugar utilisation by the tissues. This condition of course, occurs in diabetes mellitus, in which, although/

although there is an excess of blood-sugar it cannot be made use of because of the absence of insulin which renders it available for metabolism; but it has never been suggested that milk fever is in any way comparable to diabetes.

Since it is a condition necessary to the proof of the hypoglycaemia theory that the available sugar in the blood (glucose) must be low, I emphasised the difficulty of the acceptance of the theory; (121) and to this criticism Professor AUGER of the Veterinary College of Lyons (91) replied that the difficulty was capable of the following simple explanation.

As is well known, sugar exists in the blood as glucose, and in this form it is, normally, readily available to the tissues. During lactation the blood glucose is converted in the mammary gland into lactose. Lactating animals frequently reabsorb lactose from the milk into the blood (130) and the high blood-sugar found in milk fever represents, according to AUGER, a mixture of glucose and reabsorbed lactose.

Now, lactose cannot be assimilated by the tissues, therefore, it was assumed by AUGER, that although in milk fever there is admittedly an increase in the total sugar content of the blood, the actual/

actual available sugar (glucose) is deficient in amount.

At that time (1926) there was no technique known whereby the two sugars could be differentiated in the blood and AUGER'S assumption was difficult to meet; but if, as we suspected, glucose was actually present in excess in the blood, then some of this sugar should be excreted by the kidneys and appear in the urine, in which it could be identified.

I accordingly examined 14 samples of urine from 14 cases of milk fever, and in 4 (about 28 per cent.) of these glucose was obtained by the fermentation test, thus indicating the presence of excessive amounts of glucose, as distinct from lactose, in the blood.

Although these observations negated the correctness of AUGER'S opinion, they need not be discussed at further length as the matter has been conclusively cleared up by HAYDEN and FISH ⁽¹¹⁷⁾.

They, using the recently devised Folin-Svedberg technique ⁽¹²²⁾ for the differentiation of sugars in the blood showed definitely that in milk fever the great bulk of the sugar in the blood is glucose; indeed, the presence of lactose in the blood is of only occasional occurrence. Further, they showed that the increase/

increase in the blood sugar which follows mammary inflation is due very largely to lactose re-absorbed from the distended udder, and since lactose is useless to the tissues, its increase is without significance.

It can be readily understood that the administration of heavy doses of insulin to cows will produce a hypo-glycaemic coma resembling, clinically, the comatose phase of milk fever. The condition is rapidly and completely relieved by the intravenous injection of glucose; but it has yet to be shown that inflation of the udder will effect recovery in such cases.

For example, MOUSSU ⁽¹²⁰⁾ found that in an artificially produced hypo-glycaemia in the goat, mammary inflation was quite ineffective in promoting cure, but the coma disappeared and recovery rapidly followed upon the subcutaneous injection of glucose.

There is a conflict of opinion as to the value of glucose injections as a curative treatment in milk fever. As has been indicated, a few cases have been recorded in which it was claimed that glucose alone had effected recovery. In other cases glucose produced a temporary improvement in the symptoms, but resort had later to be made to mammary inflation. In still other cases glucose injections had no appreciable effect on the disease. A number/

number of precise observations upon this point are required.

In consideration of all the available evidence, it may be accepted that milk fever is not a hypo-glycaemia. An increased blood-sugar concentration is found in many intoxications, and it seems reasonable to believe that its presence in milk fever represents a natural response of the tissues in combating toxic metabolites.

ORIGINAL INVESTIGATIONS.

The original investigations which are now to be detailed were undertaken in conjunction with Dr Henry Dryerre, and a number of the results obtained have already been published in a conjoint paper.⁽¹²³⁾ The work herein described was performed by myself alone.

The technique employed, a modification of that devised by KRAMER and TISDALL⁽¹²⁷⁾, is as follows:-

COLLECTION OF BLOOD.

The/

The blood samples were collected from the jugular vein, and received direct into clean, dry bottles of 15 c.c. capacity and allowed to clot.

The serum which separated was centrifuged at 1,500 revolutions per minute for seven minutes.

Two c.c. of serum were measured into a 15 c.c. conical centrifuge tube and to this was added 1.7 c.c. of distilled water and 1.3 c.c. of a 3 per cent solution of ammonium oxalate.

The contents of the tube were thoroughly mixed by giving the tube a series of single abrupt shakes.

The mixture was allowed to stand for 45 minutes and again centrifuged at 1,500 revolutions per minute for seven minutes.

The supernatant fluid was then carefully decanted from the precipitated and packed mass of calcium oxalate, and the tube inverted upon filter paper in a draining rack and allowed to drain for five minutes.

After draining, the mouth of the tube was wiped with a clean dry cloth, and 3 c.c. of a 2 per cent ammonia solution (2 c.c. of concentrated ammonia in 98 c.c. distilled water) was run into the tube/

tube from the measuring pipette; the ammonia being introduced in such a way as to wash down the sides of the tube.

The contents were again thoroughly mixed by single, abrupt shakings.

The tube was again centrifuged for seven minutes at the same speed, and the contents again decanted and treated as before.

The washed calcium oxalate was then dissolved in 2 c.c. of approximately normal sulphuric acid, and the tube and its contents heated in a water bath at 75°C. At this temperature it was titrated against .01 N. potassium permanganate to a definite pink colour persisting for at least 1 minute.

The strength of the potassium permanganate solution was periodically checked against a standard solution of chemically pure sodium oxalate.

Throughout the course of the experiments the following points have been rigorously observed:-

- (1) All test tubes and stirring rods were prepared by -
 - (a) brush washing and rinsing in tap water.
 - (b) rinsing at least twice in distilled water.
 - (c)/

- (c) drying and polishing with a clean cotton cloth.
- (2) The burette was washed out immediately before use with the standard potassium permanganate solution. After use it was washed out with distilled water.
- (3) Throughout the whole course of the experiments the results obtained in diseased conditions have been frequently controlled by determining the concentration of blood calcium in normal animals. It may be important to emphasise that the controls have been examined concurrently with the diseased animals.

The results of the findings may be conveniently sub-divided in the following manner:-

(1) DETERMINATION OF BLOOD CALCIUM VALUES
IN PARTURIENT COWS.

Calcium is recognised as presenting less variation in quantity than any other constituent of the blood; in point of fact the serum calcium content in a given individual is singularly constant.

The calcium content of a normal milch cow is generally accepted as varying from about 9 mgrms, to 11 mgrms. per 100 c.c. serum, and an examination of the blood calcium in 16 normal bullocks and lactating cows gave an average of 10.15 mgrms; (TABLE I) but it was considered advisable to test the normal calcium values in normal cows during the usual milk fever/

fever period (i.e. within 48 hours after calving), as it has been stated that a considerable fall in blood calcium occurs at parturition.

In 18 determinations on 11 parturient cows, a range of from 8.64 mgrms. calcium to 10.97 mgrms. with an average of 9.91 mgrms. was obtained. (TABLE II).

From these figures there appears to be no difference between the calcium values in parturient cows and those in advanced lactation.

TABLE/

T A B L E I.

NON-PARTURIENT COW, & BULLOCK CONTROLS.

NO.	REMARKS	MGMS. Ca. %
1	Bullock, 2 years old	10.90
2	Bullock, 2 years old	10.70
3	Cow	9.19
4	Bullock	9.14
5	Bullock	9.80
6	Cow, pregnant	10.01
7.	Heifer, calved one month	10.35
8	Heifer, calved 8 days	10.60
9	Cow, calved two months	9.54
10	Cow, calved two months	11.11
11	Heifer, calved three months	10.40
12	Heifer, calved three months	10.70
13	Cow	10.20
14	Cow, due to calve in three weeks	9.90
15	Cow, due to calve in two months	10.39
16	Cow, due to calve in one month	9.52
AVERAGE (16 Cases)		10.15

T A B L E I I.

PARTURIENT NORMALS.

NO.	REMARKS	MGRMS. Ca. %
1.	30 hours after calving	10.18
2	14 hours after calving	10.14
3	3 hours after calving	10.55
4	A few days after calving	10.71
5	36 hours after calving	8.64
6	30 hours after calving	10.97
7	90 minutes before calving	9.52
7a	7½ hours after calving	8.79
7b	15½ hours after calving	8.84
7c	66 hours after calving	9.69
8	21 hours before calving	10.97
8a	13½ hours before calving	9.77
8b	4½ hours before calving	10.09
8c	10½ hours after calving	10.45
8d	21 hours after calving	9.41
9	Newly calved	10.24
10	9 hours after calving	9.49
11	16 hours after calving	9.9
AVERAGE (18 determinations)		9.91

(2) EFFECT OF LACTATION ON BLOOD
CALCIUM VALUES.

As has been noted colostrum is rich in calcium, and its secretion represents a heavy drain upon the tissues.

The blood volume of a cow may be taken as 7.7 per cent of the body weight.

The normal blood calcium = 0.010 per cent, of the blood.

In a 400 kilo. cow there are approximately 31 kilos. of blood and this will contain 3.1 grms. calcium.

There are 147 mgrms. calcium in 100 c.c. milk.

Therefore since 2 gallons of milk (a normal lactation) weigh approximately 8.9 kilos. this will contain 13 grammes calcium.

It therefore follows that each half gallon of milk secreted would be sufficient to deplete the blood of the whole of its calcium provided that the calcium reserves could not be promptly mobilised

(The above statement is compiled from figures given by Junk) ⁽¹³¹⁾

In/

In order to determine the effect of the initial secretion of colostrum upon the blood calcium, the following observations on two cows were made. (DRYERRE & GREIG, 'The Veterinary Record' Vol. VIII, 1928, p.723)

TABLE I.—Case No. 13, "Maisie."

1st sample	1½ hours before calving CALVED.	9.52 mgrs. calcium
2nd sample	7½ hours after calving	8.79 mgrs. calcium
3rd "	15½ " " "	8.84 " "
4th "	66 " " "	9.69 " "

Lactation commenced just after calving and was active when the second sample was taken. The figures indicate that the calcium returned to normal after the crisis accompanying the initiation of lactation was past.

TABLE II.—Case No. 15, "Hazel."

1st sample	21 hours before calving	10.97 mgrs. calcium
2nd "	13½ " " "	9.77 " "
3rd "	4½ " " "	10.09 " "
	CALVED.	
4th sample	10½ hours after calving	10.45 mgrs. calcium
5th "	21 " " "	9.41 " "

In this case a moderate lactation commenced before calving, between the collection of the first and second samples, when the calcium fell approximately by 10 per cent. It gradually returned to normal but fell again when a profuse lactation set in between the collection of the fourth and fifth samples (Fig. 1).

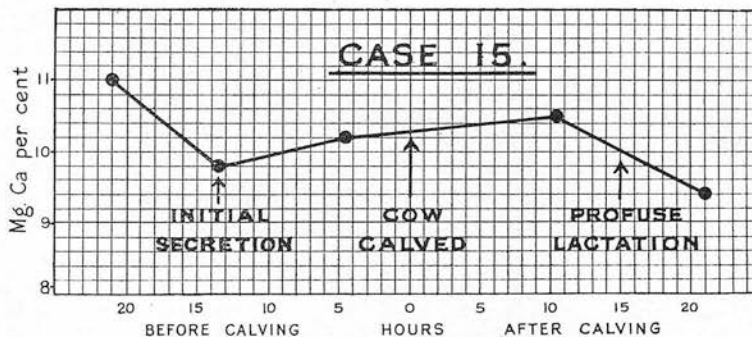


FIG. 1.—This curve shows in graphic form the data given in the preceding table.

While it would not be justifiable to draw firm conclusions from two cases, it is reasonable to regard these results as highly significant, since it would appear that the onset of milk secretion is accompanied by a transient but appreciable fall in the blood calcium which returns to normal after the crisis of initiation of lactation is passed.

(3) DETERMINATIONS OF BLOOD CALCIUM
VALUES IN MILK FEVER.

Sixty samples of blood from as many cows attacked by milk fever have been examined. Each sample was collected before inflation of the mammae with the exception of one which was obtained just after the operation had been completed. All cases appeared to be typical of the disease and responded to the classic treatment of mammary distension.

The calcium content in these cases ranges from a minimum of 3.00 mgrms. per cent. to a maximum of 7.76 mgrms. The average of the values obtained in the cases works out at 4.96 mgrms. (TABLE III).

In no case has overlapping occurred between the lowest normals and the highest milk fever calcium values.

The/

The significance of these figures is realized when they are compared with the blood calcium content of normal parturient cows; the mean of 18 determinations being 9.91 mgrms. per cent.

	MILK FEVER. (60 cases)	PARTURIENT NORMALS. (18 determi- nations)	BOVINE DIS- EASES other than MILK FEVER. (73 cases).
	Mgs. Ca. %	Mgs. Ca. %	Mgs. Ca. %
Maximal Fig.	7.76	10.97	11.71
Minimal Fig.	3.00	8.64	7.81
Average Fig.	4.96	9.91	9.40

TABLE III. TABLE II. TABLES
VII & VIII.

These results indicate that milk fever is constantly associated with a hypocalcaemia.

TABLE/

T A B L E I I I . ^{*}

M I L K F E V E R .

NO.	REMARKS.	MGRMS. Ca. %
1.	Attacked 48 hours after calving	5.89
3	Mild case	7.76
4	Mild Case	6.00
5	Mild Case	6.38
6	Mild Case. Attacked one hour after calving. Sample collected 3½ hours after attack.	7.14
7	Typical Case. Attacked 34 hours after calving.	3.77
8		4.14
9		4.09
11		4.78
12	Mild Case.	7.76
13		6.31
14	Coma: had been convulsive. Rose 4 hours after inflation.	5.27
15	Attacked 12 hours after calving.	4.24
16	Severe Case.	3.35
17	Coma.	4.86
18/		*

*

In 18 Cases (represented by the missing numbers in this series) the effect of mammary inflation on the blood calcium was observed. These Cases are described separately in TABLE V.

T A B L E I I I .

M I L K F E V E R (C O N T .)

NO.	REMARKS.	MGRMS. Ca. %
18		4.24
19		5.95
19a	Delirious (recurrence 14 days after previous attack) [not included in aggregate figure and average]	5.17
20	Attacked 18 hours after calving	5.89
21	Coma; attacked 48 hours after calving	4.65
23		4.24
25	Typical Case. During act of calving	3.72
26		4.32
27	Coma	4.03
28	Coma	7.34
30	Attacked about 24 hours after calving	6.21
31	Sample collected 4 hours after attack. Attacked 6½ hours after calving	5.79
32		5.79
33		7.03
34/		

T A B L E I I I .

M I L K F E V E R (C O N T .)

NO.	REMARKS.	MGRMS. Ca. %
34		4.96
37	Delirious; occasional unsuccessful attempts to rise.	3.62
40		4.31
41	Attacked 36 hours after calving	7.34
42	Attacked 18 hours after calving	6.52
44		4.96
45	Attacked 24 hours after calving	6.21
46	Coma; had been down for 7 hours before sample was taken, did not rise for three days after inflation	5.80
47	Coma; "down" for about $\frac{1}{2}$ an hour before sample was taken	4.65
55	Semi coma, unable to rise, attacked 24 hours after calving	7.35
56		4.99
57		4.95
58		4.85
60	(This case is described in Section 6)	5.68
	Average (42 cases)	5.41
	Average 18 cases (see TABLE V)	4.52
	Average 60 cases	4.96

Cases upon which no remark is made have been reported as milk fever by the practitioner in attendance but no further information is available.

(4) EFFECT OF MAMMARY INFLATION
ON NORMAL LACTATING EWES.

Since hypocalcaemia was found to be invariably associated with milk fever and since mammary inflation rapidly effected cure, it was necessary to determine the effect of this procedure upon the concentration of blood calcium.

I first endeavoured to ascertain the effect of mammary inflation on the blood calcium in a normal lactating animal, and the following experiments were made.

The test subjects were four black-faced ewes about six weeks lambed. The animals appeared normal, were in good milk yield, and had healthy lambs at foot.

A sample of blood was collected from each ewe. The udders of all four were then inflated, and for observational purposes the animals were divided into two groups of two ewes each. From one group (A) the blood was drawn off at intervals of half an hour, until two hours after inflation had elapsed. In this manner five samples of blood were obtained from each of two ewes, one before inflation and four subsequent thereto.

From/

From the remaining pair of ewes (Group B) the blood was sampled approximately 3, 5, 11 and 22 hours after inflation, and from each of these ewes five samples were thus obtained. These bloods were then analysed and it was found that in all the cases there was an increase of about 10 per cent. in the calcium content. In Group A the rise was observable in the specimens drawn half an hour after inflation, and it was also observed at the third and fifth hour in Group B.

These two cases indicate that mammary inflation can appreciably raise the blood calcium even in a normal lactating animal.

TABLE/



T A B L E IV.

EFFECT OF MAMMARY INFLATION
ON NORMAL LACTATING EWES.

NO.	TIME of COLLECTION.	MGRMS. Ca. %
1	12.20 p.m.	10.51
	2.45 p.m.	11.19
	5.25 p.m.	11.20
	11.0 p.m.	11.17
	10.0 a.m.	11.19
2	12.20 p.m.	10.99
	3.0 p.m.	11.61
	5.40 p.m.	10.79
	11.0 p.m.	10.27
	10.0 a.m.	spoiled
3	11.30 a.m.	10.66
	12.10 p.m.	11.17
	12.40 p.m.	10.76
	1.5 p.m.	11.17
	1.45 p.m.	10.40
4	11.50 a.m.	10.35
	12.20 p.m.	11.79
	12.50 p.m.	11.48
	1.20 p.m.	10.76
	1.55 p.m.	10.77

(5) EFFECT OF MAMMARY INFLATION ON THE
BLOOD CALCIUM IN MILK FEVER.

With the object of discovering whether there exists a correlation between the disappearance of the symptoms of milk fever and a rise in the blood calcium concentration, I resolved to make a number of serial determinations during and after the process of recovery, and 18 cases of milk fever were examined in this way (TABLE V).

It was found that inflation was invariably followed by a marked rise in the calcium concentration, and that in many cases when this reached approximately 6 mgrms. per cent. the cow attained apparent normality. In 3 cases (numbers 53, 54 and 59) the treatment consisted in injections of an organic salt of calcium. Recovery in these cases was similar to that observed after mammary inflation.

Recently SJOLLEMA⁽¹¹⁸⁾ has confirmed the finding that an acute hypocalcaemia obtains in milk fever. In an examination of 40 cases he found a calcium deficiency of approximately 50 per cent. of normal.

In one case the effect of parathyroid extract was tested. Apparent recovery was obtained within a few minutes but relapse occurred after a few hours. In 20 cases the intravenous injection of 35 to 40 grammes crystalline calcium chloride in 400 c.c. water produced rapid cure.

T A B L E V.

SERIAL DETERMINATIONS IN MILK FEVER

NO.	COLLECTIONS	REMARKS	MGRMS. Ca. %
1	1st sample (before inflation) 2nd sample 3rd sample	45 mins. after onset. Cow "down" 5 hours later. Cow now on her feet 7 days later. Complete recovery	4.14 6.00 10.04
10	1st sample (before inflation) 2nd sample 3rd sample 4th sample	Cow "down" 9½ hours later. On her feet 3 days later. Complete recovery 7 days after inflation. No recurrence	3.95 6.45 11.79 9.72
22	(before inflation) 1st sample 2nd sample 3rd sample 4th sample 5th sample	Cow tetanised but still on her feet 10 hours later. Cow apparently normal 82 hours after inflation. Complete recovery 131 hours after inflation. No recurrence 179 hours after inflation. No recurrence	5.17 8.07 10.45 11.59 9.80
24	1st sample (before inflation) 2nd sample	Cow comatose 24 hours later. Complete recovery	5.17 10.97
29	1st sample (before inflation) 2nd sample	Cow comatose 25 hours later. Complete recovery	4.55 9.23

35	1st sample 2nd sample 3rd sample 4th sample	(before inflation)	Semi-coma 4 hours later. Up; staggering 4 days later. Normal 16 days after recovery. No recurrence	3.36 6.52 8.28 10.97
36	1st sample 2nd sample 3rd sample	(before inflation)	Semi-coma 4 hours later "signs of recovery" 4 days later. Normal	3.00 5.07 10.66
38	1st sample 2nd sample 3rd sample	(before inflation)	Semi-comatose. Tetanic spasms 4 hours later, "evident signs of recovery" 4 days later, "practically normal"	5.64 11.38 8.95
39	1st sample 2nd sample	(before inflation)	"Down" 3 hours later; "on her feet"	5.27 7.24
43	1st sample 2nd sample	(before inflation)	"Down" 6½ hours later; "nearly normal"	4.55 5.81
48	1st sample 2nd sample	(before inflation)	Semi-comatose 3 days later; apparently normal	3.11 8.88
49	1st sample 2nd sample	(before inflation)	"Could stand" (Seen very shortly after onset) 48 hours later; normal	5.05 9.83
50	1st sample 2nd sample	(before inflation)	"Down"; tetanic spasms 24 hours later. Normal	5.40 8.88

T A B L E V (CONT).

NO.	COLLECTIONS	SERIAL DETERMINATIONS IN MILK FEVER REMARKS	MGRMS. Ca. %
51	1st sample (before inflation)	Semi-coma.	3.33
	2nd sample	7½ hours later, "Up but dull" and again inflated	6.64
	3rd sample	26 hours after inflation; "looks fairly normal"; severe constipation	6.66
	4th sample	54 hours after inflation. Complete recovery	10.00
	5th sample	10 days after inflation. No recurrence	10.50
52	1st sample (before inflation)	Dull, inco-ordination of hind limbs, able to walk with difficulty	3.96
	2nd sample	48 hours later, impaired appetite, still somewhat dull, otherwise normal.	6.10
53	1st sample (before treatment)	Tetanised, symptoms progressing rapidly in intensity	5.06
	2nd sample	200 c.c. calcium gluconate 10% solution injected subcutaneously immediately after collection of first sample. Second sample collected 4 hours later. Cow then normal	6.00

54	1st sample (before treatment)	Semi-coma	5.68
	2nd sample	200 c.c. calcium gluconate, 5% solution injected subcutaneously immediately after collection of 1st sample. Second sample collected two hours later, cow normal but unable to rise.	6.96
	3rd sample	Injection of calcium gluconate repeated after collection of 2nd sample. Third sample taken 4 hours later, cow still normal in appearance but unable to rise.	7.64
	4th sample	Injection of calcium repeated after collection of third sample. Fourth sample taken 14 hrs. later, cow then normal, could rise but was still unable to stand.	8.92
59	1st sample (before treatment)	Almost complete coma, calved 48 hours. 300 c.c. 10% calcium gluconate injected intravenously immediately after collection of this sample.	4.99
		Recovery rapid; cow rose and walked to her stall 75 minutes after calcium injection.	
		1½ ozs, calcium gluconate in 1 pt. water given subcutaneously to reinforce 1st injection 4 hours later.	
	2nd sample (16 hrs after 1st injection)	"Normal in every way"	6.35
	3rd sample (40 hrs after 1st injection)	"Completely recovered but suffering from acute mastitis with febrile symptoms. do.	7.92
	4th sample (64 hrs after 1st injection)	do.	8.26
		AVERAGE (18 cases)	4.52

(6) SERIAL OBSERVATIONS on the BLOOD CALCIUM
VALUES in a COW SUSCEPTIBLE to MILK FEVER,
and the EFFECTS of the
ADMINISTRATION of VITAMIN D.

So far all the analyses had been performed on bloods collected from milk fever after the onset of the disease. No information was available as to whether the fall in calcium which occurs previous to the onset was gradual or sudden.

If, in the case of a cow likely to fall a victim to milk fever, a gradual lowering of the calcium level occurred during the last weeks of pregnancy it seemed possible that this might be corrected by the administration of Vitamin D or by other means.

As has been mentioned, the disease, after the first attack, is likely to recur with each succeeding parturition, and an aged cow which had been attacked upon each of her last seven successive parturitions was selected for observation.

The first sample of blood was drawn on November 29th, 1928, and thereafter seven further samples were taken at intervals up to February 6th, 1929. During this period the calcium figures all fell within the normal range. (TABLE VII)

Just/

Just after the collection of the sample on February 6th a massive dose of Vitamin D (expressed as 50,000 Ostelin units) was given by mouth and this dose was repeated daily for 20 days. During this period 6 samples were drawn at intervals of 7, 2, 4, 3, and 4 days.

As will be seen from the table and the accompanying chart, the administration of Vitamin D was followed by a sharp rise in the blood calcium which persisted until at least the 9th day of treatment after which it fell within the normal range wherein it appeared to again become stabilised.

On February 26th the Vitamin D administration was suddenly stopped and 2 days later a marked fall occurred, the abnormally low figure of 8.45 mgrms. being registered.

Four days later the figure was again within the normal range and in this it continued until April 3rd.

The cow calved at 8 a.m. on April 2nd. and thereafter appeared to be perfectly well until 7.30 a.m. next morning when the onset of milk fever was observed. There was slight but distinct tetany of the hind limbs and difficulty in maintaining stance. Decubitus accompanied by the typical somnolence/

somnolence soon developed and, when in this condition, a sample was taken at 10.30 a.m. Convulsions were absent and sensibility was not markedly interfered with. The case was to be regarded as mild in type.

The case continued in this condition throughout the evening and night but by 6.30 a.m. next morning the cow had made a spontaneous recovery without any treatment having been applied.

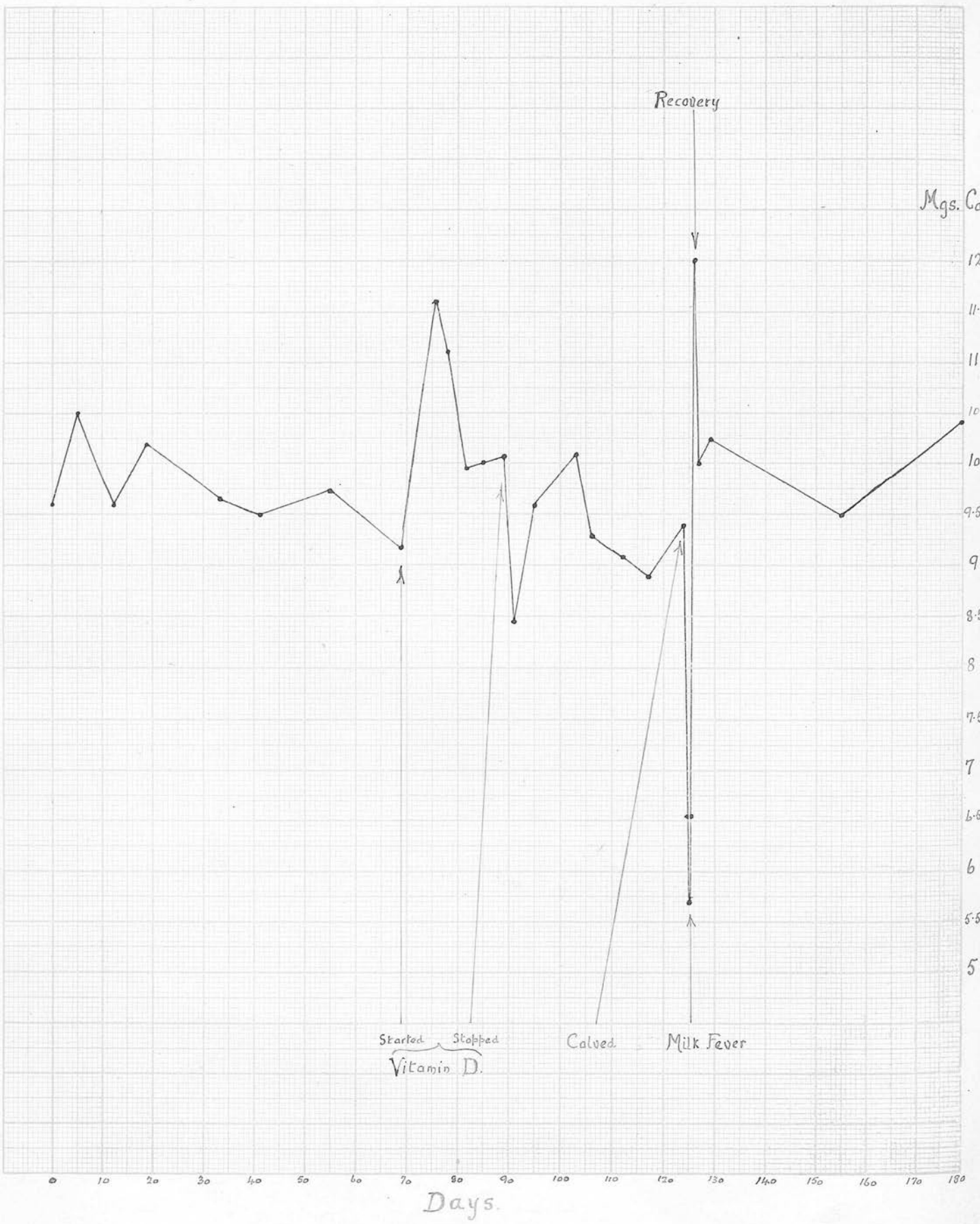
It will be observed that the calcium figures were low during the attack but upon recovery setting in they rose to a point (12.35 mgrms) much above normal; thereafter there was another steep decline to within the normal limits.

REMARKS ON THIS CASE.

This case shows very clearly that when any sudden change in the concentration of blood calcium is induced there is a tendency for an overshooting effect to occur.

For example the administration of Vitamin D in massive doses first produced a marked hypercalcaemia, but later equilibrium was established. Stoppage of the Vitamin resulted however in a well marked temporary hypocalcaemia.

Similarly/



Mgs. Ca.

Recovery

Started Stopped
Vitamin D.

Calved

Milk Fever

Days.

Similarly the onset of milk fever was accompanied by an intense hypocalcaemia and the spontaneous recovery processes not merely restored the blood calcium to normal but actually produced a temporary hypercalcaemia.

The chart as a whole suggests that there are powerful reflex mechanisms regulating the concentration of blood calcium; that these are called into play by any deviation from the normal of the blood calcium and that the compensatory mechanisms evoked are so powerful that they usually produce considerable over action.

This case also suggests that it is difficult to produce a sustained hypercalcaemia in cows by administration of excess of Vitamin D, therefore while it would appear that this agent could be effectively used as a preventive measure against milk fever it should be administered only a few days before calving.

TABLE VI.

NO.	CROSS BRED LINCOLN-ABERDEEN ANGUS COW, 18 YEARS OLD. REMARKS	UGRMS. Ca. %	COLLECTED
1		9.59	29-11-28
2		10.50	4-12-28
3		9.59	11-12-28
4		10.20	18-12-28
5		9.60	1- 1-29
6		9.49	9- 1-29
7		9.74	23- 1-29
8	Vitamin D administration commenced immediately after taking this sample	9.19	6- 2-29
9		11.51	13- 2-29
10		11.10	15- 2-29
11		9.94	19- 2-29
12		10.02	22- 2-29
13	Vitamin D administration ceased immediately after taking this sample	10.05	26- 2-29

14		8.45	28- 2-29
15		9.63	4- 3-29
16		10.09	12- 3-29
17		9.29	15- 3-39
18		9.10	21- 3-29
19		8.92	26- 3-29
20	Calved 8 a.m., sample taken 10 a.m.	9.40	2- 4-29
21	Attacked with milk fever 7.30 a.m., sample taken 10.30 a.m.	6.56	3- 4-29
22	Sample taken 2.10 p.m.	5.68	3- 4-29
--	Sample taken 6 p.m.	Spoiled	3- 4-29
23	Sample taken 9.30 p.m.	6.56	3- 4-29
24	Recovered, sample taken 6.30 a.m.	11.65	4- 4-29
25	Sample taken 4.45 p.m.	12.35	4- 4-29
26	Complete recovery; sample taken 10.30 a.m.	10.00	5- 4-29
27	No recurrence	10.50	7- 4-29
28	No recurrence	9.49	4- 5-29

(7) INVESTIGATION OF BLOOD CALCIUM
CONCENTRATION IN BOVINE DISEASES
OTHER THAN MILK FEVER.

That an acute hypo-calcaemia is constantly associated with milk fever seems to admit of no doubt, but the possibility of its occurrence as a mere concomitant was an evident possibility. I therefore considered it necessary to determine the calcium concentration in the blood of bovine animals suffering from diseases other than milk fever.

It was obviously desirable that the diseased conditions investigated should be widely representative in character, as it was my primary object to discover whether any disease was accompanied by a hypo-calcaemia comparable to that which obtains in milk fever.

No such condition was found to occur in any of the disease controls, (the results appear on TABLES VII & VIII) but because of the supposed relationship of post-parturient dyspepsia to milk fever it was considered advisable to determine the blood calcium in a large number of cases of this condition.

It may be proper at this point to describe briefly the salient features of this disease.

A SHORT ACCOUNT OF POST-PARTURIENT
DYSPEPSIA IN COWS.

Post-parturient dyspepsia although recognised since 1842 ⁽¹²⁹⁾ has been chiefly confined to the South and West of Scotland and has been of comparatively rare occurrence; but within the last few years it has become increasingly prevalent and is now commonly encountered over wide areas.

The attack, in the great majority of cases occurs during the second and third weeks after calving.

The symptoms are those of sub-acute dyspepsia accompanied by diminished milk secretion and severe constipation. The smell of acetone is very noticeable in the breath, milk and skin exhalations.

In a small proportion of cases, symptoms of spastic convulsions resembling those of acute milk fever are observed; and this, in conjunction with its association with the parturient state has led to the supposition that the disease was closely related to milk fever.

In a number of cases mammary inflation appears to cut short an attack but in other cases mammary/

mammary inflation has little or no effect.

The course usually extends over 10 or 14 days and recovery is the rule.

The disease which appears to be invariably associated with an acute hypo-glycaemia accompanied by acetonæmia is at present under investigation by Dr Dryerre, Dr Norman Wright and myself, but the results of this study of the blood calcium values, in themselves permit us to regard the disease as a pathological entity clearly distinct from milk fever.

T A B L E VII.

POST-PARTURIENT DYSPEPSIA.

NO.	REMARKS.	MGRMS. Ca. %
1	Typical	9.89
2	Atypical; dyspepsia slight; acetonaemia present	10.50
3	Typical case, but almost recovered when sample taken	10.50
4	Typical case, but almost recovered when sample taken	11.21
5	Typical	8.88
5a	Complete recovery	10.55
6	Typical	9.29
6a	Mammary gland inflated immediately after first sample taken. Second sample taken 4 hours later	9.29
6b	15 hours after inflation	9.89
6c	45 hours after inflation	9.39
6d	56 hours after inflation	10.10
7	Mild case	10.51
8	Severe typical case	10.04
8a	5 days later; complete recovery;	10.20
9	Typical	9.03
10/		

T A B L E VII (CONT).

POST-PARTURIENT DYSPEPSIA.

NO.	REMARKS	MGRMS. Ca. %
10	Severe case	9.46
11	Typical case	8.50
12	Mild case	9.74
13	Typical	9.70
14	Typical case, associated with eclamptic symptoms	8.91
15	Typical	8.63
16	Typical	8.71
17	Typical	9.10
18	Typical	9.75
AVERAGE (18 cases)		9.57

T A B L E VIII.

BOVINE CONTROLS, -
DISEASES OTHER THAN MILK FEVER.

NO.	REMARKS	MGRMS. Ca. %
1	Chronic lobular pneumonia of one month's duration	9.69
2	Abortion associated with acute septic mammitis. Semi-comatose when sample taken	8.08
3	Tuberculosis with emaciation. Heavy infestation of liver with <u>F. hepatica</u>	9.24
4	Actinomycosis	9.99
5	Abortion.	9.27
6	Abortion, one week previous	8.98
7	Abortion, three days previous	8.68
8	Calved one month; diagnosis indefinite; temp. 103° F; cough; anorexia; may be tuberculosis	7.87
9	Convulsive seizures one month after calving	10.32
10	Abortion	9.09
11	Pre-parturient paraplegia; due to calve in eleven days	8.68
11a	Three days later, Ca.Cl. 5 drachms given intravenously (no apparent response). Cow recovered 3 days later when sample was taken	9.68
12	Localised pleurisy, temp. 102.5° F. complete anorexia.	9.87
13	Acute digestive disturbance; severe tympanites; complete anorexia; stools blood smeared	8.01
14/		

T A B L E VIII (CONT).

BOVINE CONTROLS, -
DISEASES OTHER THAN MILK FEVER.

NO.	REMARKS	MGRMS. Ca. %
14	Pneumonia; temperature 107.7° F.	8.87
15	Pneumonia following "transit fever"	9.99
16	Johne's disease (chronic bacillary enteritis)	8.14
17	Tubercular mammitis	9.15
18	Abortion	9.10
19	Hydrops amnii; 5 weeks from calving; twin calves removed; collected 24 hours after operation; shock considerable	8.21
20	Acute digestive derangement	8.80
21	Acute tympanites accompanied by laminitis of both fore feet; temperature 102° F.	9.84
22	Advanced tuberculosis; generalised infection	7.81
23	Advanced tuberculosis; extensive infection	8.21
24	Miliary tuberculosis	8.71
25	Urticaria	8.16
26	Urticaria	9.40
27	Acute digestive disorder; severe diarrhoea; marked prostration.	10.69
28	Metritis of recent origin	8.81
29/		

T A B L E VIII (CONT).

BOVINE CONTROLS, -
DISEASES OTHER THAN MILK FEVER.

NO.	REMARKS	MGRMS. Ca. %
29	Metritis; old standing case	8.71
30	"Staggers"	10.66
31	Arthritis; left knee	9.52
32	Arthritis; right hock; suffering considerable pain	8.42
33	"Staggers"; calved 14 days previously	11.71
34	Tubercular pneumonia, (extensive) abdominal viscera also affected, emaciation	9.60
35	Tubercular mastitis, abdominal viscera and lungs also affected	10.93
36	Abdominal tuberculosis	10.09
37	Advanced and generalised tuberculosis	8.79
38	Cow, congestion of both lungs, temperature 106.5° F.	9.26
39	Paraplegia of unknown origin (calf)	11.08
40	Mastitis, (contagious, catarrhal)	10.14
41	" " "	10.29
42	" " "	10.09
43	" " "	10.24
44	" " "	10.44
45	" " "	10.89
46/		

T A B L E VIII (CONT.)

BOVINE CONTROLS, -
DISEASES OTHER THAN MILK FEVER.

NO.	REMARKS	MGRMS. Ca. %
46	Post-parturient paralysis	8.71
47	Mastitis	9.05
48	Heifer	10.29
49	Acute digestive disorder	8.74
50	"Stomach Staggers"	9.55
51	Convulsive seizure accompanied with severe diarrhoea.	9.60
52	"Staggers"	7.96
53	Cerebral Coeneurosis	9.35
54	Urticaria	7.87
55	Tetanus	10.04
	55 cases - average	9.34
	18 cases post parturient dyspepsia (TABLE VII) - average	9.57
	i.e. 73 cases of bovine diseases other than milk fever - average	9.40

(8) DETERMINATION of the BLOOD CALCIUM
VALUES in NORMAL SHEEP.

I have been unable to find reliable figures for the calcium content of a normal sheep, but I have examined a considerable number of healthy sheep and have found that the calcium values vary within a wide range, when compared with the other domestic herbivora.

Minimal figure 7.92 mgms.

Maximal figure 11.92 mgms.

It is possible that the lower values may be explained by assuming a calcium deficiency in the diet, since sheep frequently receive no artificial food, but are wholly dependent upon pasture for their subsistence.

My attention was first drawn to this point in the case of No.6. (TABLE IX.) which with No.5. had been grazed upon land known to be very deficient in lime.

CASES 18 to 22 were obtained from the one lambing flock. They were receiving no concentrates in their diet, and were on a pasture, the soil of which was tested (simple litmus reaction), and proved markedly deficient in lime.

The values of this group, however, show great/

great variation and, indeed, furnish both the maximal and minimal figures given above.

It is perhaps significant that during the last few years there has been a heavy incidence of milk fever among the parturient and nursing ewes on this pasture. During the past Lambing season (1929), in the flock of 370 ewes, the incidence was approximately 7 per cent. The cases, Numbers 2, 3, 4, in the ovine milk fever series (TABLE XI), were obtained from this source.

As is well known, several factors are concerned in the regulation of calcium metabolism but the possible influence of the lime content of a pasture soil in determining the calcium concentration in the blood of browsing animals, is a question of very real economic importance, which awaits investigation.

TABLE/

T A B L E IX.

SHEEP NORMALS.

NO.	REMARKS.	MGRMS. Ca. %
1	Ewe	9.69
2	Hogg	11.51
3	Hogg	11.31
4	Ewe, 3 years old	11.11
5	Ewe, 5 shear	9.49
5a	Same Ewe (repeat)	9.19
6	Ewe, 5 shear	8.08
6a	Same Ewe (repeat)	8.08
6b	Same Ewe, second sample drawn	8.28
7	Hogg	11.11
8	Hogg	10.50
9	Ewe	8.88
10	Ewe	10.10
11	Ewe	8.78
12	Hogg	9.39
13	Hogg	9.59
14	Hogg	9.99
15	Ewe	9.34
16	Hogg	8.68
17	Ewe	9.83
18	Ewe, with lamb at foot	11.92
19	Ewe, with lamb at foot	7.92
20	Ewe, due to lamb within a few days	8.51
21	Ewe, due to lamb within a few days	10.68
22	Ewe, due to lamb within a few days	9.20
AVERAGE (22 cases.)		9.80

Section 9.

Reprinted from *The Veterinary Record* 1929, *IX*, p.

(off No 96)

The Nature of Lambing Sickness.

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The Nature of Lambing Sickness.*

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Royal (Dick) Veterinary College, Edinburgh.

During the last ten years considerable attention has been directed by British veterinarians to the nature of certain diseased conditions incidental to pregnancy and parturition in the ewe.

In Scotland, at least two such conditions have gradually become recognised as distinct clinical entities, although their possible pathological relationship has been a matter of conjecture.

The diseases referred to are known as:—

(1) Pregnancy toxæmia; pregnancy disease of ewes; ewe paralysis; twin trembling; moss ill; white liver; preparturient eclampsia of ewes.

(2) Lambing sickness; ewe distemper; milk fever.

In order to avoid confusion the diseases will be referred to here as "pregnancy toxæmia" and "lambing sickness" respectively.

It is the purpose of this paper to indicate the nature of lambing sickness and to establish its identity with milk fever in the cow. There is also offered evidence by which the affection may be distinguished from pregnancy toxæmia.

PREGNANCY TOXAEMIA IN EWES.

Pregnancy toxæmia in ewes appears to have a wide distribution. Thus Gilruth describes it in New Zealand(1); Luckey(2); Hadley(3); Newson(4); Frey(5); Dimock, Healy and Bullard(6); Marsh(7); record the disease from various parts of the United States; while Bruce(8) reports it from British Columbia. There are several records of its occurrence on the Continent of Europe, particularly in Hungary(9).

In this country M'Fadyean drew attention to the malady in 1924(10), and four years later(11) Gaiger recognised the affection as widespread in Yorkshire, Lancashire and Cheshire.

My personal experience of the disease is limited to Midlothian and the Border Counties of Scotland, where its incidence has markedly increased in recent years.

* Received for publication, May 21st, 1929.

The disease appears to be confined to ewes during the last few weeks of pregnancy. Plethora is to be regarded as a predisposing factor, while the practice of heavily feeding concentrates, or alternatively, of suddenly changing the grazing ground from poor to relatively rich pasture, also increases the susceptibility to attack. In a large proportion of cases the ewe is pregnant with twins.

Symptoms.—The affected ewe separates herself from the flock. There is much depression of spirits. The head is carried in an unnatural position—it droops, is held to one side or carried very high, in which case there is usually disinclination to move. The gait becomes staggering and uncertain and, later, there is marked disturbance of vision and even apparent blindness, so that locomotion becomes blundering and erratic.

The appetite is almost completely lost and the intestinal peristalsis is sluggish if not entirely suspended. Fine tremors appear over the head and neck and may become general. The temperature is approximately normal.

In the course of a few days the ewe is found unable to rise; she lies quietly; sensibility is obviously dulled; tympanites may be extreme and is accompanied by involuntary regurgitation of ingesta from the nostrils.

Finally the animal becomes progressively comatose and death usually results in the course of one to six days. The mortality approaches 90 per cent.

On autopsy, fatty infiltration of the liver is invariably present. This condition is frequently found in healthy parturient ewes, but is particularly evident in the disease under discussion.

Dimock, Healy and Bullard (*ibid*) in a study of the urine analyses of 11 cases found that the urine is acid, contains a precipitate (presumably urates), acetone, albumen and a markedly increased quantity of ammonia.

In three cases an examination of the blood revealed a marked fall in the alkali reserve. They therefore concluded that pregnancy toxæmia represents a condition of acidosis, and suggested the name "Acidosis of pregnant ewes."

In three cases examined I was able to confirm the presence of acetonuria and, as a supplement to the work of Dimock, Healy and Bullard, I endeavoured to determine the blood calcium values which obtain in the disease.

In an examination of 22 normal sheep, of which five were parturient ewes, the following results were obtained :—

	Mgms. Calcium %
Maximal figure	11.92
Minimal figure	7.92
Average figure	10.96 9.80.

It has been found that there obtains a much wider normal calcium range in the sheep than in the cow, but the majority of the values fall within 9 mgms. and 11 mgms. per cent.

Six cases of pregnancy toxæmia were examined and gave the following readings :—

	Mgms. Calcium %
Maximal figure	10.72
Minimal figure	8.23
Average figure	9.41

It will be observed that the calcium values in pregnancy toxæmia are clearly within the normal range.

Treatment.—No curative treatment of any value is known. Mammary inflation has been repeatedly tried, but without any beneficial effect. It has been noted that in those ewes which have lambed during the course of the disease, rapid recovery followed parturition.

Prevention.—American observers claim that the incidence can be greatly reduced by exercise (driving the ewes slowly but continuously over a distance of two or three miles daily). In this country the most practical means of prevention consists in reducing the food of the ewes that have not yet lambed to a bare subsistence limit.

In my experience the adoption of this procedure, which was strongly advocated by M'Fadyean, has immediately cut short several extensive outbreaks of the disease.

DISCUSSION.

The apparently constant acetonuria and the observed acidosis suggest an investigation of the blood glucose concentration as a fruitful line of enquiry. A series of controlled observations on the therapeutic effect of injections of glucose and insulin as a means of indicating the origin of the ketosis further suggests itself.

LAMBING SICKNESS.

Since 1903, when Hewetson(12) first drew attention to a peculiar affection of lambing ewes which resembled milk fever in the cow, the disease variously known as "lambing sickness," "ewe distemper," "milk fever," has become generally recognised over large areas, especially in the Midlands and North of England and in the Border Counties of Scotland.

References to the disease in veterinary literature are few, Cundell(13), Walpole(14), Masson(15), Armstrong(16), Gunning(17), and this may be partly accounted for by the comparative rarity with which veterinary practitioners are called upon to undertake the treatment of sporadic cases of disease in sheep.

Shepherds, too, have learned that inflation of the mammæ is rapidly followed by complete cure, and they themselves commonly practise this treatment.

There has been much speculation as to whether milk fever in the cow, and lambing sickness should be regarded as representing a single pathological entity. They are similar in their time relationship to parturition, although lambing sickness not infrequently appears shortly before lambing, and is also commonly encountered in ewes with young lambs at foot. Cases also occur in ewes in advanced lactation, especially if grazed on strong pasture. Similarly so-called "delayed milk fever" may attack non-parturient, lactating cows which have been run on succulent pasture, and it has been noted that such animals are specially susceptible to attack during œstrum—a fact which may be correlated with the known influence of ovarian secretion in lowering the blood calcium.

The clinical symptoms of lambing sickness and milk fever in the cow also present much similarity, and the response to mammary inflation is common to both; but since the

pathology of neither was known their relationship could only be suspected.

Upon its becoming evident that milk fever in cows was invariably associated with an acute hypocalcæmia(18), I resolved to determine the calcium values which obtained in lambing sickness.

Very great difficulty was experienced in obtaining material, but I have been able to examine the bloods from five cases.

A summary of the analyses is set out in the following table:—

	Mgms. Calcium %
Maximal figure	5.94
Minimal figure	3.51
Average figure	4.40

It will be observed from the above figures that an acute hypocalcæmia is present in lambing sickness.

In three cases the effect of mammary inflation on the blood calcium has been observed:—

Case No.	Remarks.	Mgms. Ca. %
2	Before inflation, comatose ...	3.52
	Two hours later, apparent recovery	7.05
	Fifteen hours after inflation, normal	7.17
	One week later, complete recovery	9.69
3	Before inflation, semi-coma ...	4.35
	Twelve hours later, normal ...	6.71
4	Before inflation, deep coma, collapse, " apparently at the point of death "	3.51
	Two hours later, " quite lively, run- ning about freely " ...	7.73
	Fourteen hours after inflation, " quite normal "	7.82
	One week later, complete recovery	9.80

The rapidity with which recovery follows mammary inflation can properly be described as amazing, and the concurrent rise in blood calcium is no less remarkable.

In Case No. 4 the collapse was so extreme that, upon a cursory examination, the ewe was at first believed to be dead.

In one case (No. 1) the practitioner in attendance, Mr. Oscar Stinson, obtained a rapid recovery by means of a subcutaneous injection of calcium gluconate(19).

DISCUSSION.

Apart from the similarity between milk fever in cows and lambing sickness, in their conditions of occurrence and in their clinical manifestation, the acute hypo-calcæmia which obtains in both diseases and the intimate relationship which exists between the progressive rise in blood calcium and the corresponding and concurrent disappearance of the symptoms which follows the mechanical distension of the mammæ, justifies the conclusion that lambing sickness and milk fever in cows may be regarded as identical in their essential pathology.

In an examination of 100 cases of various diseased conditions (68 in cattle, 32 in sheep) the calcium values have been found to be either normal or somewhat diminished. In no case, so far examined, has there been found a hypo-calcæmia in any way comparable to that which occurs in milk fever in cows and lambing sickness in ewes.

There is no doubt that very large numbers of cases of lambing sickness are not recognised as such and are allowed to die.

That an acute and pronounced hypo-calcæmia is the prevailing factor in milk fever may now be regarded as established, but it is reasonable to suppose that so great an upset in the mineral balance as must be occasioned by the sudden fall of calcium must result in severe disturbances in general metabolism, which have their reflex in the complicated milk fever syndrome.

Acknowledgements.—I am gratefully indebted to the following gentlemen for assistance in obtaining material :—Mr. N. Bisset, Mr. A. Edgar, Mr. O. Stinson, Mr. H. B. Allan and Professor S. H. Gaiger.

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The above paper forms part of a general investigation on milk fever which the author is prosecuting in collaboration with Professor Henry Dryerre and Dr. N. C. Wright, by the aid of grants received from the Development Commission, and the Highland and Agricultural Society of Scotland.

(9) THE BLOOD CALCIUM CONCENTRATION
IN LAMBING SICKNESS.

I have examined the calcium concentrations which obtain in a number of diseased conditions in sheep, and the results of an investigation into the nature of Lambing Sickness have already been published. A copy of the paper is enclosed herein, but the results may be briefly summarised as follows:-

In an examination of 22 normal sheep of which five were parturient ewes, the following figures were obtained:-

	MGMS. CALCIUM %
Maximal figure	11.92
Minimal figure	7.92
Average figure	9.80

Six cases of pregnancy toxæmia were examined and gave the following readings:-

	MGMS. CALCIUM %
Maximal figure	10.72
Minimal figure	8.23
Average figure	9.41

It will be observed that the Calcium values for pregnancy toxæmia are clearly within the normal range.

Analysis of blood from five cases of lambing sickness revealed the presence of an acute hypocalcaemia. A summary of the results is set out in the following table:-

	MGMS. CALCIUM %
Maximal figure	5.94
Minimal figure	3.51
Average figure	4.40

In those cases examined, it was found that following treatment by mammary inflation, the recovery was rapid and was associated with a concurrent rise in the blood calcium concentration.

The following is an example:-

CASE NO. 4.

Immediately before inflation, deep coma, collapse - "apparently at the point of death".	3.51
Two hours later - "quite lively, running about freely".	7.73
Fourteen hours after inflation - "quite normal".	7.82
One week later, - complete recovery	9.80

The possible relationship between lambing sickness and milk fever is discussed, and it is concluded that the two diseases possess the same essential pathology.

T A B L E X.

PREGNANCY TOXAEMIA

NO.	MGRMS. Ca. %
1	8.23
2	9.79
3	9.70
4	10.72
5	9.11
6	8.91
AVERAGE (6 cases)	9.41

T A B L E XI.

MILK FEVER IN EWES.

NO.	REMARKS	MGRMS. Ca. %
1	Comatose	4.70
2	Comatose, inflated immediately after sample taken	3.52
2a	2 hours after inflation, apparent recovery	7.05
2b	15 hours after inflation, normal	7.17
2c	One week after inflation, complete recovery	9.69
3	Semi-coma	4.35
3a	12 hours later, normal	6.71
4	Deep coma; collapse "apparently at the point of death"	3.51
4a	Two hours after inflation "quite lively, running about freely"	7.73
4b	14 hours after inflation "quite normal"	7.82
4c	Collected one week later, complete recovery	9.80
5	Pregnant ewe due to lamb in 7 days time	5.94
AVERAGE (5 cases before inflation)		4.40

(10) THE CALCIUM CONCENTRATION IN CERTAIN
DISEASES IN SHEEP OTHER THAN MILK FEVER.

It was hoped to obtain blood samples from a representative collection of cases of sporadic ovine diseases but the lack of veterinary contact with sporadic diseases of the sheep to which reference has already been made, proved a serious difficulty.

It was however found possible to determine the blood calcium concentration in a number of cases of scrapie (TABLE XII) and louping ill, (TABLE XIII) two diseases the etiology of which is obscure.

The evidence shows that although the calcium concentration in advanced cases of scrapie, especially those associated with debility, tends to be low, no acute hypocalcaemia obtains in either disease.

As has been shown, the calcium values in pregnancy toxaemia of ewes also fall within the normal range (TABLE X).

T A B L E XII.

SCRAPIE.

NO.	REMARKS	MGRMS. Ca. %
1	Ewe	8.33
2	Ewe	9.79
3	Ewe	9.59
4	Ewe	9.69
5	Ewe	9.59
6	Tup, about two years old	10.35
7	Ewe, about three years old	9.69
8	Ewe	9.34
9	Ewe	10.10
10	Ewe, advanced stage of disease	8.38
11	Ewe, advanced stage of disease	8.18
12	Ewe, advanced stage of disease	8.58
13	Ewe, advanced stage of disease	8.88
14	Ewe, severe case	9.19
15	Ewe, severe skin irritation	9.60
16	Ewe, severe skin irritation	8.18
17	Ewe, severe skin irritation	9.64
18	Ewe, comparatively mild case, (early stage)	10.25
19	Ewe, early stage	11.51
AVERAGE (19 cases)		9.41

T A B L E XIII.

LOUPING ILL.

CASE NO.	REMARKS	MGRMS. Ca. %
1	Ewe, severe case	11.53
2	Tup lamb, lightly affected	9.99
3	Ewe lamb, lightly affected	11.68
4	Lamb, 14 to 18 days old; severely affected	12.37
5	Tup lamb, typical case	10.54
6	Tup lamb, lightly affected	10.79
AVERAGE (6 cases)		11.15

(11) DETERMINATION of BLOOD CALCIUM VALUES in
NORMAL HORSES.

An examination of the blood calcium values of 25 normal horses, gave an average reading of 12.99 mgms. per cent (TABLE XIV). This corresponds with the findings of MONTGOMERIE, SAVAGE & DODDS (128) who obtained an average of 13.00 mgms. per cent in six examinations.

TABLE/

T A B L E X I V .

H O R S E N O R M A L S .

NO.	MGRMS. Ca. %
1	10.76
2	10.66
3	12.21
4	12.12
5	12.62
6	14.64
7	13.83
8	12.32
9	13.83
10	13.63
11	14.34
12	13.73
13	14.94
14	13.13
15	13.13
16	13.33
17	12.82
18	13.02
19	13.13
20	12.62
21	14.14
22	12.32
23	12.52
24	13.13
25	11.90
AVERAGE	
	12.99

(12) DETERMINATION of the CALCIUM VALUES in
TRANSIT TETANY IN HORSES.

An interesting condition manifested by tetany, occurs in lactating mares which have been closely confined in travelling by rail or sea. It has also been observed in mares during oestrus.

A considerable degree of trismus is almost invariably present, but the condition can be readily distinguished from tetanus, by the suddenness of the manifestation, and by the absence of protrusion of the the membrana nictitans which is almost pathognomonic of tetanus in the horse.

HARVEY (126) observed that this form of tetany in lactating mares, somewhat resembled milk fever, and he found that cure could be readily obtained by mammary inflation.

A large number of cases terminate fatally, and SAVAGE (128) has noted a mortality of over 60 per cent.

MONTGOMERIE, SAVAGE & DODDS (128) found that in two cases the calcium values were 5.20 mgms. and 6.20 mgms, per cent. They also found a marked rise in the phosphorus and in the alkali reserve.

In 5 cases recovery followed the subcutaneous injection of air.

transit I have had opportunity to examine two cases of tetany and can confirm the calcium findings of MONTGOMERIE, SAVAGE & DODDS; the values being found as follows:-

PONY NO. 52. 4.85 mgms. per cent

PONY NO. 54 5.38 mgms. per cent.

The affected animals were two of a lot of ponies, which had been shipped from the Shetland Isles to Leith, and were suckling foals of about a month old.

NO. 52 received Mammary inflation.

NO. 54 was treated by injecting subcutaneously 200 c.c. of a 10 per cent solution calcium gluconate.

Within a few hours both ponies were appreciably improved and within twelve hours were apparently normal. Recovery was uneventful.

Further work is required upon the nature of this disease, as at present it is difficult to explain the effect of travelling in lowering the blood calcium. The effect, if any, of the subcutaneous injection of air upon the level of blood calcium, also awaits investigation.

(13) DETERMINATION of BLOOD CALCIUM VALUES in
GRASS DISEASE in HORSES.

The name "Grass Disease" has been given to a disease which attacks horses at pasture during the summer grazing period.

The etiology is quite obscure, and is at present the subject of much intensive study and an examination of 18 cases shows no abnormality in the blood calcium concentration.

TABLE/

T A B L E XV.

GRASS DISEASE.

NO.	MGRMS. Ca. %
1	11.90
2	12.42
3	12.73
4	12.93
5	13.04
6	12.83
7	8.59 *
8	12.74
9	13.04
10	12.42
11	12.42
12	12.10
13	12.83
14	13.97
15	13.04
16	13.86
17	14.28
18	14.49
AVERAGE	12.75

* No particulars of this case obtainable.

DISCUSSION.

The evidence elicited by this investigation has established that a constant association exists between an acute deficiency of the blood calcium and the manifestation of the symptoms of milk fever, and on the following considerations it is reasonable to believe that the hypocalcaemia is the causal factor and not a mere concomitant.

- (1). Milk fever is invariably associated with an acute hypocalcaemia.
- (2). The more severe cases correspond with the lower calcium values.
- (3). The fall in calcium is approximately coincident with the appearance of the symptoms.
- (4). Tetany is a cardinal symptom in the early phase of the milk fever syndrome and the occurrence of tetany is recognised as consequent upon pronounced hypocalcaemia.
- (5). Mammary inflation raises the level of blood calcium in a normal lactating animal.
- (6). Mammary inflation elicits a marked rise in the level/

level of blood calcium in milk fever and cures the disease; the process of cure, as manifested in the disappearance of the symptoms, corresponds with the rise of the blood calcium.

(7). Injection of calcium, exclusive of other treatment, raises the blood calcium concentration and cures the disease.

(8). Milk fever in cows, lambing sickness in ewes, and transit tetany in mares are all rapidly cured by mammary inflation and these are the only conditions in an examination of about 350 samples of blood in which an acute hypocalcaemia has been found.

The calcium content of the blood has been previously studied with reference to chronic diseases such as rickets, but the diseases herein described are acute and the falls of blood calcium are relatively enormous.

The level of blood calcium shows a remarkable constancy throughout all the vertebrates; fishes, amphibians, reptiles, birds and mammals have all a concentration of about 10 mgrms. calcium per cent.

Experiments on isolated tissues of the most diverse/

diverse kinds show that any variation in the calcium content of the perfusion fluid profoundly affects their function. A fall of calcium to half its normal value is sufficient to account for most marked effects.

As is well known calcium deficiency produces hyperexcitability of the neuro-muscular mechanism manifested by tetany. While there is no direct evidence that calcium lack paralyses the brain, there is the indirect evidence that injections of magnesium produce anaesthesia and this effect is abolished by calcium.

The syndrome of milk fever could be reasonably explained by the excessive fall in calcium; the tetany, the weak and accelerated pulse, the intestinal stasis, the ultimate coma and paralysis could all be attributed to an acute and profound hypocalcaemia.

The assumption that the curative effect of mammary inflation lies in preventing milk secretion and the consequent exchange of calcium from the blood to the milk seems to offer the only plausible explanation of the phenomenon; that mammary inflation does arrest milk secretion is well recognised for the adoption of this treatment seriously interferes with the re-establishment of lactation after recovery/

recovery from the disease.

It is for this reason that practitioners have frequently expressed a desire for some form of treatment which could effectually substitute mammary inflation, and it has now been shown that this can be obtained by the intravenous injection of calcium compounds.

The observed effects of the administration of Vitamin D on the blood calcium values (Section 6) suggests that the disease might be prevented by the repeated administration of massive doses of the vitamin for 4 or 5 days previous to parturition, so that during the milk fever period (48 hours after calving) the blood calcium concentration would be high.

Alternatively, this could probably be effected by daily flooding the blood with calcium by the intravenous injection of some assimilable calcium salt.

CONCLUSIONS.

- (i). There is no difference between the calcium values in parturient cows and those in non-parturient cows and in bullocks.
(Section 1)
- (ii). The onset of milk secretion is accompanied by a transient but appreciable fall in the blood calcium which returns to normal after the crisis of initiation of lactation is passed. (Section 2)
- (iii). In milk fever there is, invariably, a pronounced fall in the blood calcium. The degree of severity of the symptoms is in inverse ratio to the calcium level in the blood. (Section 3) From a series of observations made in one case, before and during the attack, the fall in calcium appears to be abrupt; it is coincident with the onset and corresponds with the progressive severity of the symptoms. (Section 6)
- (iv). Inflation of the mammae of normal lactating ewes/

- (iv). ewes causes a rise in the blood calcium (about 10 per cent.) (Section 4)
- (v). Inflation of the mammae of the cow in cases of milk fever results in a pronounced rise in the blood calcium. The rise is at first rapid, and the case usually shows definite signs of recovery when a level of about 6 mgrms. of calcium per cent. has been reached. (Section 5)
- In mild cases which recover spontaneously (one case observed) it would appear that the rise in calcium is as rapid as when inflation is practised. (Section 6).
- (vi). In three cases of milk fever the therapeutic effect of injections of calcium has been tested. In each case recovery was rapid. (Section 5)
- (vii). In a study of the effects of Vitamin D on the level of the blood calcium, it was found that the daily repeated administration of the vitamin in massive doses was followed by a sharp rise in the calcium which/

(vii). . . which persisted for about nine days.

The sudden cessation in the vitamin administration was followed by a marked drop in the calcium level. (Section 6)

(viii). In a large number of examinations of diseased conditions in cattle other than milk fever, none was found to present a hypocalcaemia in any way comparable to that which obtains in that disease.

A comparatively slight but notable hypocalcaemia was observed to be associated with debilitating diseases such as tuberculosis and chronic bacillary enteritis. (Section 7)

(ix). The blood calcium values of normal sheep were observed. It would appear that the normal variation of blood calcium is greater in sheep than in cattle.

The findings also suggest that the calcium content of the pastures may influence the blood calcium concentration. (Section 8.)

(x). The association of acute hypocalcaemia
with/

- (x). with lambing sickness was determined.
(Section 9)
- (xi). The known curative effects of mammary inflation in lambing sickness have been found to be correlated with a rise in the blood calcium values. In one case the therapeutic effect of subcutaneous injection of calcium was tested: the treatment resulted in rapid recovery. (Section 9)
- (xii). In a consideration of the clinical and experimental evidence, it is concluded that milk fever and lambing sickness possess the same essential pathology. (Section 9)
- (xiii). An examination of ovine diseases other than lambing sickness failed to reveal any condition of hypocalcaemia comparable with that disease; although certain cases of scrapie, in an advanced stage of cachexy, presented low calcium values. (Section 10)
- (xiv). The calcium values of normal horses were found to be considerably higher than those of cattle and sheep. (Section 11)
- (xv)./

- (xv). In an examination of two cases of transit tetany in mares a pronounced hypocalcaemia was found. (Section 12)
- (xvi). In one case of transit tetany, mammary inflation, and in the other calcium injection was followed by complete cure. (Section 12)
- (xvii). The blood calcium concentration in grass diseases in horses was found to be undisturbed. (Section 13)

A C K N O W L E D G M E N T S .

The author wishes to express his grateful thanks to Professor A.-J. CLARK, B.A., D.Ph., Department of Pharmacology, Edinburgh University, who has freely given much valuable advice and encouragement during the course of the investigation.

His thanks are also due to his colleague Dr. Henry DRYERRE, from whom he received instruction in the technique of calcium analysis, and with whose close collaboration the hypothesis of hypocalcaemia upon which this research is based, was first evolved.

The collection of a large number of blood samples was rendered possible by the willing help of many veterinary practitioners; while these are too numerous for individual mention, special reference should be made to Mr Oscar STINSON, M.R.C.V.S., Appleby, and to Mr William KENDRICK, M.R.C.V.S., Tarvin, who supplied much material.

Thanks are also due to Principal O. Charnock BRADLEY, and to the Board of Management of the Royal (Dick) Veterinary College for laboratory facilities.

Much difficulty arising from lack of financial assistance, was experienced in the earlier part of the work, but this has now been overcome by grants/

grants received from the Development Commission
and the Highland and Agricultural Society of Scotland.

I declare that the work described in this
Thesis has been performed by myself alone.

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