THE AETIOLOGY AND CHANGING INCIDENCE OF CONVULSIONS IN CHILDHOOD

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C O N T E N T S

P R E F A C E

To-day is the day of team-work in research and the clinician must combine with the biochemist, pathologist, statistician and even physicist in order to contend with the problems of medicine in our atomic age. It may therefore seem foolhardy to attempt a survey that is at once historical, statistical, biochemical and clinical. Nevertheless though the methods are diverse the scope of the investigation is small for I am concerned with the meaning of a symptom in paediatrics.

This investigation is in many ways a continuation of the work on convulsions by Professor Stanley G. Graham to whom I am grateful for suggesting the topic and also for ever present encouragement and unstinted advice. The cases studied were all in Professor Graham's wards at the Royal Hospital for Sick Children, Yorkhill and the estimations were performed in the hospital laboratory. I would express my gratitude to Dr. H. Ellis Wilson and his colleagues for the hospitality of their work-bench. I should also like to thank Dr. D. Campbell Suttie and his staff for access to records.

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The main part of this thesis is as yet unpublished but "The Historical Background" with only slight modification is appearing in the Archives of Disease in Childhood.

The Aetiology and Changing Incidence of Convulsions in Childhood

Part I

A CRITICAL REVIEW

I The Historical Background

II The Twentieth Century

I - THE HISTORICAL BACKGROUND

Convulsions in childhood must be as old as mankind and it would be remarkable if so striking and terrifying an affliction had not received attention of one kind or another throughout the ages. In so far as the attitude of a community to a convulsion is merely a reflection of its attitude to medicine and an indication of its scientific and ethical background, the history of convulsions can only be in essence the history of medicine or, as we are only concerned here with children, of paediatrics. It may however be of some interest to trace briefly the evolution of the present-day conception of convulsions in childhood against the historical background.

Although the civilisations of Egypt and Babylon, and Brahaminical medicine in India appear to have had more or less enlightened views on the upbringing of children, little can be discovered of their precise attitude to convulsions. It is nevertheless likely that they all shared to some extent the view that a convulsion was due to direct divine intervention or demoniacal possession, a view that lingers even to-day in the words "epilepsy" and "seizure". In ancient Egypt this idea was carried to the extreme of holding all disease and even death to be due to the intervention of external agents (Finlayson): these agents might apparently belong to this or the "other" world. Thus where the intervention was not obviously of this world/

world, such as an assassin or a falling tree, the physician had the double duty of identifying the offending spirit and thereafter of prescribing the specific treatment. Usually amulets and incantations were regarded as indispensable.

European medicine begins properly in Greece. The achievements of Athens in the time of Pericles are perhaps the most astonishing in all history. Under the stimulus of victory over the Persians she produced architects, sculptors and dramatists who remain unsurpassed to the present day. It was at this time that Hippocrates, who was thus a contemporary of Socrates and Plato, lived and taught. Born in this era of untrammelled philosophical speculation Hippocrates' genius presents a remarkable difference from that of his illustrious contemporaries; for he was the first to treat of medicine as a practical study rather than as a speculative philosophy. His was a method of observation and inductive reasoning so ideally suited to clinical medicine. His writings deal with medicine, surgery, midwifery, embryology, climatology, dietetics, prognostics and ethics but not specifically with paediatrics. There are however numerous pertinent observations in his general writings and in particular his well-known treatise on "The Sacred Disease" or epilepsy. He differentiated between epilepsy and infantile convulsions but the distinction, as we might expect is not clear.

In the "Aphorisms" he points out that teething is associated/

associated with a number of unhappy afflictions including diarrhoea and convulsions, this particularly at the time of the eruption of the canines and in fat constipated infants. Thus originated a belief that over two thousand years of medical progress have not quite eradicated. He also stated that those who were afflicted with the "falling sickness" before the age of fourteen might become free of it but those who were affected at the age of twenty-five were usually troubled with it to the end. A more important observation on infantile convulsions occurs in "Prognostics" (chapter XXIV) and is worth quoting verbatim (Adams' translation):

"Now in children convulsions occur if there has been acute fever, and if the bowel has not been open, and if they have been sleepless, and if frightened, and if they have been screaming, and if they have changed colour acquiring a greenish or pale or livid or red colour. Convulsions occur most readily from first after birth up to the seventh year. But older children and men are no longer liable to convulsions in fevers, unless some complication with violent and very grave symptoms has arisen, as, for example, happens with acute delirium." This it will be seen epitomises fairly well the views on infantile convulsions held until the end of the nineteenth century.

In discussing epilepsy Hippocrates derided and rejected the view of those he termed "the ancients" that the condition had/

had a supernatural cause as implied by its name. He attributed the disease rather to a specific pathology of the brain, namely, the obstruction by phlegm of the air (sic) in the veins of the brain. He also described the aura of true epilepsy.

The importance and greatness of Hippocrates in the history of medicine lies not in the detail of his conclusions, though many of these alone would entitle him to be remembered, but in his method of clinical observation and in his insistence upon the natural origin of disease. It is one of the ironies of history that almost all that was sound in his teaching was forgotten while the dross was handed down reverently through the ages to smother independent thought.

Aristotle, the most versatile of all philosophers, also has a place in the history of convulsions. His father, a court physician, must have spoken often of the great physician Hippocrates who died when Aristotle was only fourteen. The medical writings of Aristotle, such as they are, for he was no physician, are at least reminiscent. In Book 7 (which is devoted to Man) of his treatise "On the History of Animals" he writes:-

"Children are very subject to spasms especially those that are in good condition and have abundance of rich milk, or whose nurses are fat. Wine is injurious in this complaint, and dark coloured wines more so than those that are pale ..... " He further/

further points out that these children usually die before the seventh day and it is for this reason that the naming of the child is postponed until then.

With Aristotle closes the period of Grecian greatness in philosophy and medicine and with his pupil, Alexander the Great, begins the Hellenistic age famed for its mathematics and science. The brief career of Alexander transformed the Grecian world. In the third century B.C. the Greek city-states came to an abrupt end with the rapid growth of the Macedonian Empire but meanwhile the Roman Empire was beginning to take form and in the second century B.C. Greek medicine emigrated to Rome. There was no Roman tradition in medicine and indeed, before the Greek influx, Rome had "got on for 600 years without doctors" according to the elder Pliny.

Although medicine was practised almost exclusively by Greeks, the best account of it comes from the pen of a Roman. Aurelius Cornelius Celsus is a subject of much controversy. He is usually said to have lived during the reign of Tiberius Caesar, step-son of Augustus, and to have been a Roman Gentleman and not a physician. As to the first, Still would place him earlier, in the reign of Augustus, thus making him a contemporary of Virgil, Livy and Horace. As to the second, this is most vehemently denied by his translator, Grieve, as also but with more evidence by Still. His are the earliest medical records extant after the Hippocratic writings to which he shows great/

great deference. Although he is the first to state that children should be treated entirely differently from adults, he left no paediatric writings and as regards convulsions dealt specifically only with epilepsy. His views differ little from those of Hippocrates. He emphasised that convulsions may cease at puberty and advocated some rather startling remedies including the drinking of the blood of a newly-slain gladiator. Should these remedies be of no avail he tells us, the condition will probably last throughout life which is not thereby shortened.

Soranus of Ephesus who lived in the second century is the leading authority upon obstetrics and gynaecology in antiquity. He was also a paediatrician and the latter part of his work upon diseases of women is apparently devoted to infant welfare and the treatment of the commoner diseases of infancy. I have unfortunately been unable to obtain a copy of this but in the list of contents given by Still there is no mention of convulsions or epilepsy.

The ancient period closes with the name of the greatest and most influential Greek Physician. Galen who lived from 131 to 201 A.D. founded a system of physiology, pathology and pharmacy which dominated Europe up to the time of Vesalius in the 16th century. At the age of thirty-four he settled in Rome to become court Physician to Marcus Aurelius. He was a prolific writer/

writer but included little of paediatrics. In his De Sanitute Tuenda he treats of infant hygiene. There is also a discourse on an epileptic boy for whom he recommends purgation and squills together with full directions as to diet and physical exercise. In a lesser known work "On Medical Experience" he exemplifies the importance of sequence in symptomatology thus:-

"If, for example, convulsion follows fever, this is a sign of death and if fever follows convulsion, this is a sign of safety." Galen's importance lies in the wide acceptance which his attitude of mind to natural phenomena commanded. Gone was the clinical observation of Hippocrates, gone was the imaginative freedom of thought, the heritage of the Greeks. For Galen crystallised Greek thought into a rigid system that explained everything and the ingenuity of physicians of the next fifteen hundred years was exercised in the Procrustean task of fitting observed facts to his principles. The next six centuries saw the fall of the Western Roman Empire and the establishment of the Byzantine Empire in the east which was to last another thousand years. The degeneration of the Roman Empire into a great unwieldy administrative machine in which nearly every one of education was a civil servant gave it little strength to repel barbarians from the north. Meanwhile the Christian Church was growing rapidly into a vast and inflexible hierarchy and attracted all the outstanding minds to her service. Already torn and buffeted within by theological controversies/

controversies and obsessed with the problems of heresy she looked askance at all original thought and laid the foundations for an age of ignorance, superstitition and unspeakable cruelty which was to last over a thousand years until the renaissance. In this mental climate it would have been extraordinary had there been any outstanding contributions to medicine. The only name of importance is that of Paul of Aegina who lived from 625-690 A.D. He was the last of the Greek eclectics and his emphasis that his work is not original but that of a mere scribe penning the thoughts of the masters is a sign of the times. He has nothing much to add to his predecessors; again he emphasises the importance of dentition in convulsions and tends to minimise the importance of epilepsy in children. He recommends attention to diet and also the changing of a wet nurse in cases of infantile convulsions. Here he foreshadows views on the dangers of breast milk which are carried to fantastic extremes in the eighteenth century.

The Eastern Empire was also subject to repeated attacks but while that of the west was attacked by northern barbarians who became Christians in the process, that of the east was attacked by Mohammedans who developed an important religion and culture of their own. Moreover, the religious tolerance of their régime attracted many persecuted Christians from the west, although admittedly, by the simple expedient of a tax, large numbers were enticed into the fold of Islam. The Arabian school of medicine which here grew up became the most enlightened/

enlightened of its time and two Persians are noteworthy, Rhazes in the ninth century and Avicenna in the tenth.

Rhazes was the first to devote an entire treatise to the diseases of children and his writings were still quoted as authoritative in the fifteenth and sixteenth centuries. A beautiful vellum-bound copy of a Latin translation of his works, printed in Venice in 1503, is to be found in the Library of the Royal Faculty of Physicians and Surgeons in Glasgow. The treatise De egritudinibus puerorum is quite short and the chapter De epilepsia puerorum is but a paragraph of Hippocratic orthodoxy. The next chapter also quite short is entitled De quadam passione quae dicitur mater puerorum. This is the first mention of a strange term which was later used frequently for anything from epilepsy to "night-terrors." In Arabian medicine it appeared to mean convulsions as opposed to epilepsy. Rhazes cites the usual causes of infantile convulsions as the cause of mater puerorum. Later it appears to mean the same as epilepsy (Mercuriale and Roelans) while later still it was used more in the sense of "night-terrors" in children and globus hystericus in adults. Hence King Lear (Act II, sc. IV)

O! how this mother swells up toward my heart;
Hysterica passio! down, thou climbing sorrow!

Avicenna more famous as a philosopher though renowned as a physician as well, wrote largely of infant hygiene in Canticum/

Canticum de Medicina. In Canonis Medicinae he lists the diseases of infants with little more than a statement of their occurrence and advocates most drastic remedies such as bleeding and cupping, all directed at the unfortunate wet-nurse. He attributes the convulsions of dentition to fermentation in the gut and, of course, quotes Hippocrates.

The Dark Ages which followed added little to medical knowledge although the famous school of Salerno in the ninth century and that of Montpellier in the twelfth may be mentioned. It was the invention of the printing press in the middle of the fifteenth century that paved the way for the renaissance with which our modern history begins. The change in mental outlook which characterises this period was determined by the diminishing authority of the church and the increasing authority of science. Temporal authority was now vested in the state with a result that the culture of the period was more lay than clerical and moreover, this lay culture was less subject to supervision and direction by the state than that of the middle ages had been by the church. The authority of science however, came much later than the rejection of the authority of the church; there was nothing scientific in the Italian renaissance. The advance of medicine therefore lagged rather behind and it need not surprise us to find that the earlier works printed have much in common with that of the Greek eclectics and tend

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to be commentaries upon the Greek and Arabian schools of medicine but more enlightened commentaries perhaps. Three paediatric incunabula of this period are worth a more detailed study; the first by Paolo Bagellardus, the second by Bartholomaeus Metlinger and the third by Cornelius Roelans. One may mention an anonymous little book which was often quoted by Roelans and is attributed by Sudhoff to the twelfth century, named "Diseases of Children Still in the Cradle." This is entirely therapeutic and recommends for epilepsy peony grass and the curdled milk of a hare.

Bagellardus was the author of the first printed text-book of paediatrics entitled Libellus de egritunibus infantum and dated 1472. The first part is devoted to child care and the second to diseases in which he treats of epilepsy and convulsions of children. On epilepsy he cites both Hippocrates and Avicenna and emphasises its danger at an early age: "If it happen at birth, it is not to be cured, or scarcely ever." In nurselings the treatment is directed at the unfortunate nurse and the list of dietary restrictions to be imposed upon her would daunt the most altruistic of souls. For older sufferers the materia medica is as picturesque as ever and ranges from the mere suspension of an emerald round the neck to the drinking of the dust (sic) of a burnt "prickly pig." It is hard to see in what way/

way convulsions should differ from epilepsy but it would seem from the short description he gives of convulsions that these were attacks of rigidity or even opisthotonos rather than clonic convulsions. The pathogenesis is Hippocratic but the treatment is dramatic. "Yet I know from experience that I have seen many infants so stiff that they could not be bent upward or downward, who, by the mere application on the spondyles of the neck of oil of white lilies or wet hyssop, are relieved and cured by the favour of the Lord from such a contraction."

The next year saw the publication of another paediatric treatise but this time in the vernacular. Metlinger wrote Ein Regiment der jungen Kinder with the same respectful obeisance to the classic authorities demanded by custom but the obeisance is perhaps a little more formal and even casual. In the section devoted to disease he deals only with convulsions and although there is much of the familiar galenical therapeutics a breath of realism pervades the whole chapter. "It should be known that when convulsions affect a child soon after birth it generally dies. My advice is to protect the children with the help of God. Children may die from this but one should protect those that come later." "It is advised that the nursing woman behave herself, avoid sin, avoid eating apples, be clean and not give the child too much at a nursing but little and often."

Cornelius/

Cornelius Roelans is the author of a rare incunabulum which was unknown until exhumed by Sudhoff. An almost identical text however, was published a hundred years later by Sebastian of Austria under his own name. Roelan's book has no title page but begins with a preface in which he modestly styles himself "aggregator" or compiler. He cites a formidable array of authorities and lists fifty-two diseases in descending order from head to foot. He also deals with both epilepsy and "spasms." If any authorities preponderate in his compilation it is perhaps those of the Arabian school, Avicenna and Rhazes.

The sixteenth century is of much more interest to the paediatric historian and among a galaxy of names who contributed to the advance of medicine at that time, one Guillaume de Baillou or Gulielmus Ballonius, wrote on convulsions. He was the first to describe whooping-cough and the first epidemiologist of modern times. He is also author of one of the first medical dictionaries. Although he wrote towards the end of the sixteenth century, his works were published only some considerable time after his death. In De Convulsionibus, written in 1587, we have the same constant reference to the ancient masters while a combination of the view held by Hippocrates that the nasal discharge of coryza, or pituita, comes directly from the brain, with that of the cerebral origin of convulsions, leads rather interestingly to a suggestion of the pathological basis for the association

of/

of convulsions with respiratory infections.

Also to this period belong Sebastianus Austrius, who plagiarised the works of Cornelius Roelans, Hieronymus Mercurialis and Scévole de Ste. Marthe. Of Sebastian of Austria, although his works were republished a hundred years later interlarded with prolix commentaries by Nicolas Fontanus and therefore presumably regarded as of some importance, little more need be said; the last word is with the masters. Mercurialis writing towards the end of the century, shows more originality of thought but with no particular reference to convulsions. Scévole de Ste. Marthe might also be passed over but for the remarkable form in which his treatise on children, Paedotrophia, was written. A Latin epic upon the care of children would seem to be in a strange medium. More remarkable still is its apparent popularity at this time. It was twice translated into English in verse. The sole contribution to the study of convulsions that he makes is the elegant presentation of an inelegant remedy, namely, the powdered ash of human skull.

The sixteenth century also saw the publication of the first book on the diseases of children written in English. The earliest edition extant of "The boke of children" by Thomas Phayer or Phaer is dated 1545 (the edition consulted, 1546). The fame of Thomas Phayer as a lawyer and a physician was almost eclipsed by his renown as a poet but his medical works nevertheless occupied an important place in the medical literature for/

for the next half century. He devoted one chapter to the "falling-evil called in the greek tongue epilepsia." As to aetiology he states that it is "sometimes by nature received of the parents, and that it is impossible or difficile to cure, sometime by evil and unwholesome diet, whereby there is engendered many cold and moist humours in the brain." Otherwise he is largely concerned with prophylaxis and treatment. For the former he recommends as charms to be hung round the neck, "mistletoe of the oak taken in the month of March, and the moon decreasing" and "the stone that is found in the belly of the young swallow being the first brood of the dame." In his therapeutics one feels that the poet has as much to say as the physician: one should give with water and honey, the "maw of leveret", powdered root of peony, or "the purple violet that creepeth on the ground in gardens and is called in English, 'heartsease'."

On the whole the sixteenth century was more occupied with theology than with science. In medicine there was little more than some crude theorising and meagre observation. The scientific awakening that followed the religious liberation of the renaissance was largely of the seventeenth century, culminating with the publication of Newton's Principia in 1687. Réné Descartes who is regarded as the founder of modern philosophy also contributed to modern science and in particular to physiology. It is as a philosopher however, that he has had most influence on medicine and science in general. His break/

break with the scholasticism of the past and his examination de novo of the problem of existence paved the way for a rational investigation of the phenomenal world.

The great advances in every direction of human activity during the seventeenth century permit only of passing reference. The names of Kepler, Galileo and Newton in science, Descartes, Hobbes, Spinoza and Locke in philosophy, and Sydenham, Harvey and Glisson in medicine are eloquent of the greatness of this period. Of those concerned with children in general and convulsions in particular, a more detailed consideration may be of interest. Nicolas Fontanus may be dismissed as belonging at heart to a former century. Similarly J. Starsmare whose "Children's Diseases" published anonymously in 1664 contains nothing new in the conception of convulsions except an ill-defined relationship to the phases of the moon.

Robert Pemmell, a practitioner in Cranebrook in Kent was the author, a hundred years after Phayer, of the second book on diseases in children published in English. The full title of this book, including as it does an apologia, is worthy of reproduction.

"De Morbis Puerorum, or a Treatise of the Diseases of Children with Their Causes, Signs, Prognosticks, and Cures, for the benefit of such as do not understand the Latin Tongue, and very useful for all such as are House-keepers and have Children." In his chapter on "The Falling Sickness or Convulsion" he does not differentiate between epilepsy and convulsions and lists/

lists among the possible causes, "corruption" of the milk "which does often happen when the nurse is of ill complexion," also worms, smallpox, measles or other fevers. Some cases may be hereditary or due to "vehement pains of the teeth," "sudden fears" or a thrashing. Of more interest are his comments upon phlegm (presumably upper respiratory infection) as a cause. "Some will have phlegm to be the cause of Falling Sickness; but if it were so, then why might not old men (whose brains are phlegmatic) have the Falling Sickness .... : Therefore the Falling Sickness doth not proceed from phlegm, but rather from an occult and sharp quality, which doth oppress the membranes of the brain. For although children do abound with phlegm, (from whence suffocating rheums and other diseases be bred) yet doth not the Falling Sickness follow except there be some venomous and corrupt vapour joined therewith.

There follow also a few pertinent remarks in the chapter upon dentition where he quotes Hippocrates as authority for citing teething as a cause of convulsions. He reiterates the danger of this period and à propos lancing of the gums he is "confident that the want hereof doth occasion the death of many a child."

In 1667, Thomas Willis, the celebrated author of Cerebri Anatome, wrote at some length upon the subject of convulsions. Here for the first time we have a logical approach to the problem. He deals largely with epilepsy but/

but comments that in children the term 'convulsions' is usually employed. To convulsions in childhood he devotes a separate chapter. Epilepsy may be hereditary or acquired, primary or sympathetic. It is primary when the brain is first affected and sympathetic when the brain is drawn into sympathy with other parts of the body such as the stomach, spleen, uterus and intestines. He also differentiates between what we would term grand mal and petit mal. The immediate cause of epilepsy he gives as an "inordinate motion of the spirits in the brain."

He finds convulsions in children to be most common in the first month of life and during dentition. The prognosis is by far the worst in the newborn. He distinguishes two kinds of convulsion in children. The first might be called toxic and he includes those caused by excessive heat or cold, dietary excesses, changes of air and by the sudden disappearance of an exanthem. The second might be termed reflex and he attributes these to irritation of peripheral nerves such as by milk curdled in the stomach, worms or teething. He describes in some detail how dentition causes convulsions reflexly. The growing tooth causes pressure on the fifth nerve and so presumably stimulates the brain. With regard to treatment, he advocates lancing of the gums, or "friction" and also purging, enemata, bleeding and vesicants. His appreciation of the value of post-mortem examination and his truly scientific approach to the interpretation of his results are/

are a notable advance.

1689 is an important landmark in the history of paediatrics. So far there had been no generally accepted text-book of paediatrics written by a physician. Walter Harris supplied this want and his book De Morbis Acutis Infantum became the standard work on the subject and remained so, being translated into English in 1742, until the appearance of Underwood's treatise in 1789. As the relationship of teething to convulsions will play an important part in tracing the modern views on convulsions from this time onwards it is of interest to quote Harris verbatim (Martyn's translation): "Of all the Disorders which threaten the Lives of Infants, there is none that is wont to produce so many grievous Symptoms as a difficult and laborious Breeding of Teeth." Apart from dentition he makes no reference to aetiological factors in convulsions except one that he styles hereditary and which is apparently limited to the newborn. He attributes this to a "Foulness contracted in the Womb."

The eighteenth century which virtually begins in the final decades of the seventeenth, was a period of relief and escape; relief from the strain of a mysterious universe. Pope's oft quoted couplet well illustrates the feeling of the times:

Nature and Nature's laws lay hid in night:
God said, Let Newton be! and all was light!

To quote Basil Willey, "Nature's laws had been explained by the/

the New Philosophy; sanity, culture, and civilization had revived; and at last, across the gulf of the monkish and deluded past, one could salute the ancients from an eminence perhaps as lofty as their own." The tempo of advance in science and medicine was now increasing. Observation and experiment was laying the foundation of modern medicine. One has only to mention some of the names, Linnaeus, Rutherford, Priestley, John and William Hunter, Auenbrugger, Heberden, Pott, to illustrate the greatness of this century.

It is thus with rather a sense of disappointment that one reads the chapter on convulsions in Underwood's "A Treatise on the Diseases of Children" published in 1789. For Underwood's text-book remained the authoritative work on the subject for over sixty years and is certainly in style and mental approach, the forerunner of the modern scientific text-book. He first describes convulsions as being of two kinds, symptomatic and idiopathic, the latter being due to a morbid affection of the brain. He doubts himself, however, the validity of this distinction and is inclined to call all convulsions, in infancy at least, symptomatic as one can usually find in every case, a cause. Of these causes the most important are teething and alimentary irritation and he instances indigestibility of food and intestinal parasites and even "wind" as potent causes of convulsions. In addition he attributes some cases to a dangerous quality of the breast milk which can be caused apparently by emotional changes/

changes in the mother or wet-nurse and he gives an example of a woman who had a fright and who thereupon suckled her child which straightway had a fit. For treatment he recommends purges, enemata and bleeding.

Another famous work is Baumes' Traité des Convulsions dans l'Enfance written in 1805. He believed convulsions to be largely constitutional and attributable to "les facheuses impressions de l'air." The "curdled breast milk" is given great prominence and he instances the child of a colleague who had a convulsion after sucking at the breast of its nurse who had immediately before been very angry. The choicest anecdote is that of a woman who, knowing apparently of the dangers to her child, after having lost her temper suckled her little dog; the dog at once had a fit. All views are carried to extremes and he described convulsions of such violence as to break bones and lacerate tissues. He treats at great length of diet and hygiene as prophylactic measures. He also lists every known helminth as a cause of convulsions and would differentiate between the syndromes produced by each worm.

John Burns included a chapter on diseases of children in his text-book of midwifery and gynaecology in 1814. He classified convulsions into those due to a primary affection of the brain, e.g. hydrocephalus, and those in which the affection of the brain is "in sympathy" with some other organ in/

in a state of irritation. The causes of the "irritation" are the usual ones and he includes Baumes' impure air. He also includes trismus of the newborn as due to constipation though states that others believe it to be due to an infection of the umbilicus.

The next important contribution was that of John Clarke in 1814. His "Commentaries on some of the most important diseases of children" contains the first clear cut clinical description of tetany including laryngismus stridulus, carpo-pedal spasm and convulsions. Although no aetiological basis could be given for this condition, the separation of one group of convulsions on clinical grounds marked an important step in their classification. In addition there is a long chapter on infantile convulsions. He comments upon the large number of children shown as dying of convulsions in the London Bills of Mortality but points out that terminal convulsions are not uncommon in infancy and that the probability is that a large number of deaths are so recorded whereas the underlying condition is not noted. Thus we have two clear cut classes of convulsions separated from the main body, the convulsions of tetany (though not, in fact so-called until named by Corvisart) and the non-specific terminal convulsions.

In 1826 John North published his "Practical observations on the convulsions of infants." He lists as the main/

main causes of convulsions "large or enlarging heads," "rachitis" and "hereditary predisposition" and this is the first record that I have found of rickets being a cause of convulsions. However the fundamental cause is the greater sensitivity of children. This sensitivity is apparently greater in the tropics and he quotes a colleague, one Dr. Hillary, who "observes that the children in the Isle of Barbadoes are so irritable that they are thrown into a convulsion at the slightest noise." Loss of consciousness is not essential to the diagnosis of convulsions which he differentiates from epilepsy in which loss of consciousness is the rule. From this he goes on to the pathological fantasy that epilepsy is derived from the brain and its membranes whereas simple convulsions come from the cord. Simple convulsions he divides into symptomatic and idiopathic though he also doubts the latter. He finds convulsions occur seldom at night, a fact that he attributes to there being fewer stimuli. He comments upon a marked increase in the incidence of convulsions and attributes it to over education. At this time children were given advanced teaching at a very much earlier age than to-day. His causes of the symptomatic convulsions are the usual ones such as teething and constipation, though he castigates Baumes for his emphasis on helminths as a cause. He mentions however that in Germany the current opinion was that children rarely if ever suffered from the effects of dentition. He also describes carpo-pedal

spasm/

spasm as a prodromal sign of convulsions. He perpetuates the idea of harmful breast milk as a cause but the suggestion that suckling during menstruation may cause convulsions, he tells us "requires no further notice than the mention of its absurdity." In addition he derides the common superstition in nurses that constipation in an infant denotes strength and advocates a purgative in all cases. He has two new aetiological factors for convulsions of the newborn, retention of meconium and the shining of too bright a light on the child immediately after birth.

In the next thirty years such text books as those of Evanson and Maunsell in Dublin, and Radcliffe continue in much the same vein. Towards the end of the nineteenth century however, the tempo of scientific advancement was accelerating to reach the breathtaking speed of the present day and the greatness of the fin-de-ciècle may properly be taken as the beginning of the modern period.

In 1859 Kussmaul and Tenner described some important observations on the pathogenesis of convulsions. As a result of various animal experiments to determine the relationship between haemorrhage and convulsions, they concluded that convulsions might be produced by (1) rapid loss of blood, (2) sudden stoppage of flow of arterial blood to the brain such as produced by ligature, spasm, inflammation, or excitement, (3) rapid transformation of arterial blood to venous as in asphyxia, which of course, would explain the association/

association of convulsions with laryngismus stridulus. They further conclude that some cases of epilepsy may be caused in this way.

In 1862 Trousseau published his Clinique Médicale de l'Hôtel-Dieu de Paris. Although he devotes a great deal of space to the consideration of tetany including of course a detailed description of the sign that goes by his name, he does not relate it in any way to infantile convulsions. Indeed there is a lot that is already very familiar in his description of infantile convulsions. He classifies them as idiopathic or symptomatic, the former showing no discernible pathological change in the central nervous system except some congestion which he regards as secondary. Otherwise we have the predisposing factors of heredity, underfeeding, haemorrhage, high fever, exposure to cold or emotional upsets, and above all, local irritation including ill-fitting clothes and sinapism. The symptomatic convulsions are due either to demonstrable disease of the central nervous system or in sympathy with disease in some other part of the body such as the exanthemata.

The most impressive article of this period is one by Hughlings Jackson that appeared in Reynold's "System of Medicine" in 1868. Jackson emphasises that a convulsion is a symptom and not a disease and this, though apparently simple, is a most important advance in our understanding of the problem. For consideration he divides convulsions into those affecting children up to seven years of age and those affecting/

affecting children over seven.

On convulsions in the former age group he says they differ from adult convulsions only in the immaturity of the nervous system and he considers them as equivalent to delirium in adults. He cites cerebral haemorrhage as a cause of convulsions in the newborn. He condemns the use of the terms "essential" or "idiopathic" convulsions or eclampsia for he believes these convulsions to differ in no essential from epilepsy. He describes crowing and carpo-pedal spasm in convulsions but while he admits that these occur more frequently in rachitic children he includes them with other localising indications as a manifestation of the site in the brain of the nervous discharge. Hughlings Jackson is of course, responsible for the conception of epileptic discharge and that the site of maximal discharge would determine the type of manifestation at the beginning of the attack. This as Symonds points out was intended to apply to epilepsy as a whole and not only to traumatic epilepsy which he used however to illustrate his point. It seems particularly unfortunate that the term "Jacksonian epilepsy" was used to denote epilepsy arising from a macroscopic pathological focus in the brain when no such restricted concept was intended by Jackson. He was concerned with the localisation of the lesion and not with its pathology and would, one feels sure, have agreed that the commonest cause of a Jacksonian attack is idiopathic epilepsy. He next makes the/

the vitally important point that such factors as over-eating, worms and teething will not produce convulsions in a healthy nervous system. He does not try to differentiate between eclampsia (or idiopathic convulsions of childhood) and epilepsy but points out that many epileptics give a history of convulsions in childhood which had been disregarded. For treatment he condemns the routine use of purges, emetics and lancing of gums and rather doubtfully allows their use if there is an obvious indication.

The experimental work of Soltmann in 1876-78 is of great importance in the study of convulsions in children. He was the first to approach the problem of the greater susceptibility of children to convulsions experimentally. He demonstrated in animals aged one to ten days, that stimulation of the cortex produced no result whereas there was hyper-excitability of the peripheral nerves. He reckoned the ten days to be the equivalent of six months in man and postulated immaturity of the nervous system with failure of the reflex inhibiting motor centre of the brain. This was an important physiological observation but the corollary that any peripheral "irritation " might therefore be responsible for a convulsion seems decidedly retrograde, particularly in the light of the previous work of Hughlings Jackson. However, Soltmann's views did not pass unchallenged and Fleischmann made the pertinent observation that in burns - an especially striking form of "peripheral irritation" - convulsions did not occur, while Henoch pointed out/

out that the liability of children to convulsions was not limited to the first six months or even the first year of life.

Henoch was a pupil of Schönlein and one of the principal German contributors to Paediatrics. In his "Lectures on Children's Diseases" he discusses the pathology of convulsions in relation to the recent work of Kussmaul and Tenner and also suggests head injury as an occasional cause with extravasation of blood into the medulla. In repeated convulsions however he recommends examining the bones for "according to my experience, the tendency to convulsions is favoured by nothing so strongly as rickets." In children with convulsions aged six months to three years, rickets was usually more or less marked and laryngismus either concomitant or alternating with the convulsions, almost constant. He considers rickets to be more important than dentition in this connection. In reflex causes he places irritation of the gut first though he had seen no case that could be attributable to worms. In convulsions associated with a febrile illness he suggests an analogy with the rigor of an adult. In addition he points out that any fit may be the first sign of epilepsy.

Gowers in 1893 defines epilepsy as the result of the tendency of the brain to discharge and separates other convulsions arising from causes other than primary states of the brain, under the head of eclampsia though he specifically excludes from this the "single fit at the onset of an acute infection/

infection or in consequence of an indigestible meal." He attributes the special liability of children to eclampsia to the non-myelinated state of the nerve fibres and to the fact that the lower centres in childhood are further advanced than the higher controlled centres. However, he goes on to say that the next most potent cause is rickets (then of course regarded as a "constitutional" disease of unknown aetiology) and attributes to rickets the majority of so-called teething convulsions. He notes the association of carpo-pedal spasm and laryngismus with rachitic convulsions. He accepts however gastro-intestinal irritation by indigestible food or worms as a cause.

Paul Simon writing in Grancher, Comby and Marfan's text-book in 1898, also criticises Soltmann's theory on the ground that as all children do not have convulsions though they are all exposed to some degree of the peripheral irritation that should cause them, there must be some specific predisposition. This he suggests may be hereditary or due to debility especially of the nervous system as in prematurity, artificial feeding, haemorrhage, intestinal flux, congenital syphilis and rickets. He denies that teething is ever a cause of convulsions but cites temper at being thwarted as one.

Now for the first time there begins a real enquiry into the prognosis of infantile convulsions and their relation, if any, to epilepsy. In 1843 Rilliet and Barthez put the question without coming to any very definite conclusion. Infantile convulsions/

convulsions may or may not be epileptic and time alone will tell. Bouchut in 1855 believed all infantile convulsions to be incidental and with a good prognosis. So also D'Espine and Picot (1877) who deny the relation of eclampsia (or infantile convulsions) to epilepsy, terming the former "un accident éphémère." On the other hand Comby in 1897 and Féré in the same year called all infantile convulsions epileptic. They both stressed the importance of heredity as an aetiological factor and Comby while accepting as precipitating factors dyspepsia, gastro-enteritis, rickets and eruptive fevers and pneumonia, doubted the importance of dentition. In America, Walton and Carter (1891) joined the optimists and concluded that "epileptics are at least no more likely to have had infantile convulsions and conversely a child suffering from infantile convulsions is no more likely to suffer from epilepsy in life after a period of immunity has removed the case from the class of epilepsy beginning in infancy and becoming continuous."

II - THE TWENTIETH CENTURY

INTRODUCTION

With the turn of the century our historical survey merges imperceptibly into a review of the recent literature - and there is a considerable overlap between that which properly belongs to history and that which is of direct importance to our thesis. The amount that has been written on the subject of convulsions in infancy and childhood during the last forty-eight years is of course enormous and very much more has been written on epilepsy alone than on the convulsions of infancy. It has in fact been impossible to avoid reviewing a number of papers devoted entirely to the nature of epilepsy. This is not only because epileptic convulsions are often recognised in children but because the nature of infantile convulsions and the extent to which they are fundamentally epileptic are inseparable problems. Likewise the nature of epilepsy itself becomes relevant to our argument.

In surveying the literature as a whole one can discern three main preoccupations; the epileptic origin of all or nearly all convulsions, tetany or spasmophilia and the separate identity of the convulsions of infancy. One might almost extend the analogy of contemporary philosophical argument and dub them Monist, Dualist and Trinalist schools of thought! Although I would not by any means insist upon this classif-

ication nor/

nor upon the last dubious neologism, it will be useful to try and reduce to some semblance of order that which would otherwise be a heterogeneous catalogue of opinions bearing no relation to each other but that of chronology.

THE SEPARATE IDENTITY OF INFANTILE CONVULSIONS

It is convenient to take the last first and discuss the theme of "Gelegenheitskrampf" which runs through German literature up to the present time. The first systematic study of convulsions in infancy and childhood to be published apart from the standard text-books was by Hochsinger in 1905. He is responsible for the concept of a benign non-recurrent convulsion associated with disease in childhood and which is related neither to epilepsy nor to tetany. These convulsions he called "Gelegenheitskrämpfe". There is no precise English equivalent of this term though perhaps "casual convulsions" on analogy with casual labourer (Gelegenheits-arbeiter) comes nearest to it. I shall use the word "Gelegenheitskrampf" in this review untranslated and according to Hochsinger's definition: "By 'Gelegenheitskrampf' one can designate shortly that form of convulsion which occurs in an acute or subacute disorder of health (Gesundheitsstörung) and in which the child in the non-convulsive period shows no signs of hyper-excitability of the central nervous system." Hochsinger divided infantile convulsions into (I) Incidental Convulsions (Die/

(Die Gelegenheitskrämpfe der Kinder) and (II) Convulsions of Hyper-irritability. This classification he elaborated unnecessarily by the inclusion of unrelated myotonias and by the subdivision of tetany into its various manifestations.

The concept of "Gelegenheitskrämpfe" accords well with Soltmann's theory (page 23) of hyperexcitability and peripheral irritation of the nervous system in infancy. Soltmann's theory however, did not go unchallenged and Thiemich (1906), one of the most important names in the study of infantile convulsions, marshalled arguments against him. He pointed out that the most severe examples of peripheral irritation met with in childhood such as burns, scalds, peritonitis and ulceration of the intestines were not often accompanied by convulsions. Nevertheless Thiemich did not on that account deny the existence of "sogennanten 'Fieberkrämpfe' und andere 'Gelegenheitskrämpfe' im Sinne Hochsingers."

Reflex convulsions arising from minor peripheral irritation were an accepted entity in Britain and Hutchison (1911) vied with Baumes (page 22) in detailing their causes. Hutchison seemed to except the convulsion that ushered in an acute infection and dismissed it as the equivalent of a rigor in an adult. In this connection one may mention that Kleinschmidt (1929) studied the incidence of rigors in children and found them occasionally even in the first and second year of life; they were usually associated with an acute infection.

Guthrie (1913) believed that the gamut of causes of peripheral/

peripheral irritation caused a lowering of health and a consequent instability of the nervous system. However "it is only in the minority that peripheral irritation is the sole cause of convulsions." He made the point that teething was only associated with convulsions if it were painful as when the gums were unhealthy. Husler (1920) also believed in a true "Gelegenheitskrampf" and emphasised its initial character and its separateness from epilepsy. "Die Gelegenheitskrämpfe sind weder echte epileptische Krämpfe, noch sind ihre Träger später Epileptiker geworden." Sachs and Hausman (1926) after pointing out that healthy children were as exempt from convulsions as healthy adults, championed with vigour reflex irritation as a cause of infantile convulsions: "of the influence of two conditions there can be no reasonable doubt. These two are dentition and gastro-intestinal irritation." In spite of the objections of paediatricians who point out the association with rickets and tetany they maintained that convulsions occurred in the absence of these two conditions and further pointed out that the cutting of teeth was a direct irritant to the fifth nerve.

Cross (1928) advocated a simple pathogenesis and simple treatment for infantile convulsions. Pyrexia either from rickets or some other cause excited the nerve cells of the cortex. In so doing it damaged them so that they were permanently disordered and epilepsy resulted. Reduction of the temperature (by cold baths) stopped the convulsion and prevented/

prevented recurrence. Faerber (1929) alleged that these convulsions were not all as benign as they were reputed to be. Cameron (1929) reiterated the reflex causes of convulsions especially colic and teething. Wyllie (1929) lengthened this list to include indigestion, phimosis and foreign bodies in the external auditory meatus; this even in a healthy baby.

Catel (1932) discussed the hyperexcitability of the infant's nervous system and compared the newborn child to a decerebrate animal witnessing the abnormal reflexes, Babinski and Moro, of this period. The convulsions of infancy were therefore to be regarded as physiological.

Zappert (1932) in a long and scholarly review of convulsions and epilepsy in childhood accepted the concept of "Gelegenheitskrampf" only to a limited extent. He would limit it to convulsions accompanying acute infections and would prefer the term "Infektkrampf". The analogy of the rigor he considered to be without justification and moreover he would include convulsions as late as the fourth or fifth day of illness.

Monrad (1932a) described what he called an Initial Fever Convulsion but he described in addition "neurogenic" convulsions which were the reflex convulsions of peripheral irritation. Rather remarkably he cited burns and injuries as causes of reflex convulsions and he dignified colic with the name of "colica flatulenta."

Lederer (1934) doubted the independent existence of the "Gelegenheitskrampf." So/

So also did Eckstein (1934) who wrote "jeder Fieberkrampf eine Epilepsie einleiten kann, doch handelte sich hier eben nich um eine genuine, sondern um eine symptomatische Epilepsie." Indeed he felt that the more we learn of organic disease of the brain the less shall we speak of "Gelegenheitskrämpfe." Later he puts this more pithily: "Gelegenheitskrampf ist ein Verlegenheitsdiagnose." With this Stauder (1939) is in full agreement.

Herlitz (1941) is the only writer of recent years who has studied de novo the nature of the "Gelegenheitskrampf" or what he styles "Die sogennanten Initialen Fieberkrämpfe bei Kindern." This paper contains a great deal that is relevant to the present study and it will be necessary therefore to review it in greater detail. Over a period of five years he collected from five hospitals for children, the records of 776 children who had had a convulsion on falling ill. The table of causative diseases is interesting and is reproduced in Table I. He investigated the question of how often these convulsions really were initial and found that in only 14% of cases did the fit arise within two hours of the first symptom. In 60% of cases however, it occurred within the first twenty-four hours. The average age was eighteen months. The oldest case was nine and a half years old. Of the causative diseases he found acute pharyngitis by far the most frequent. He excluded the convulsions of whooping-cough from consideration believing them to have an encephalitic origin. His main thesis rests/

TABLE I

Disease	Number of cases
Acute pharyngeal infections	618 (79.6%)
Acute pulmonary infections	45
Acute gastro-intestinal disease	31
Vaccination fever (without clinical encephalitis)	7
Clinically certain encephalitis	11
Laryngitis acuta, bronchitis acuta, inflammation of the urinary tract, erysipelas, urticaria and sunburn	22
Infectious diseases	20
Unknown infections	22

rests upon the temperature findings. He found the progress of the temperature characteristic of the initial fever convulsion to be a rise a few hours before the fit, reaching a maximum at a time approximately coinciding with the onset, only to fall more rapidly thereafter. The risk of convulsion increased with the height of the fever and the rapid fall explained the cases in which the temperature was normal. With regard to seasonal incidence he criticised the views of Graham (1932, 1933) and believed the apparent peak in the spring to be due to the seasonal incidence of the causative disease. He expressed the number of convulsions admitted each/

each month as a percentage of the total febrile illnesses and found a slight rise in incidence in the summer. He therefore claimed that the initial fever convulsion had a seasonal incidence with a peak in the summer unlike that of tetany in the spring. He concluded that these convulsions were neither spasmophilic nor epileptic and neither were they encephalitic nor the equivalent of a rigor.

Crump (1945) investigated the incidence of convulsions in the various conditions in which these were liable to occur. He found the lowest incidence (7.0%) in cases with acute infections exclusive of meningitis, and the highest in tetany (89.5%) while 54.8% of cases of meningitis had convulsions.

Livingstone, Bridge and Kajdi (1947) made a special study of those children in whom the first convulsion was associated with an acute febrile illness. These were separated into two groups, those in whom each convulsion was associated with an acute infection and those in whom the first convulsion was, but later convulsions were not. Taking a criterion of cure as two years freedom from convulsions, all of the first group but only 37% of the second group were cured. They suggested a significant difference between the hereditary factors which predispose to chronic epilepsy and those which predispose to childhood convulsions.

SPASMOPHILIA OR TETANY

Great emphasis was laid upon tetany as a cause of convulsions/

convulsions in infancy by Thiemich (1906) who also described a late form occurring in older children. This he called "Späteklampsie" and he defined it thus: "Krämpfe, die auf dem Boden der spasmophilien Diathese entstehen, und sich von den gewönlichen eklamptischen Anfällen der ersten Kindheit nur durch das höere Alter der betreffenden Kinder unterschieden. Sie sind meist, aber nicht immer die Wiederholung der Saüglingskrämpfe. Sie gleichen der Epilepsie vornehmlich dadurch, dass sie im 5 bis 8 lebensjahre (vielleicht auch noch später) auftreten, unterschieden sich aber von ihn durch das Vorhandensein ausgeprägter tetanoïder Symptome und durch die günstige Prognose." Indeed he regarded tetany as one of the commonest causes of infantile convulsions. He also commented upon the marked seasonal incidence of cases of tetany and demonstrated a peak in March. He published a table showing the seasonal incidence of 245 cases. Still (1912) also stressed the importance of tetany. Redlich (1911) on the other hand did not accept the distinction between tetany and epilepsy which he considered more apparent than real. Graetz (1913) reviewed the same question and concluded with Sir Roger de Coverley that much might be said on both sides. Guthrie (1913) attributed the convulsions of rickets and tetany to the intestinal toxaemia which accompanies these conditions while in the convulsions of tetany an asphyxial factor was added. In this connection Robertson (1924) attributed epilepsy to intestinal toxaemia. Gebhardt (1918) investigated the electrical/

electrical reactions of older children with so-called initial-fever convulsions and found most of them to be spasmophilic. Curschmann (1918) postulated an endocrine aetiology of convulsions on analogy with parathyropriva tetany. Karger (1919) wrote on the subject of terminal convulsions and believed them to have nothing in common with tetany or other symptomatic convulsions. Husler (1920) criticised Gebhardt's views on the spasmophilic origin of initial-fever convulsions. Neither would he accept Thiemich's "Späteklampsie". Likewise Husler and Spatz (1924) investigating the convulsions of whooping cough denied their relationship to tetany in spite of the presence of rickets in many of them. They cited two cases in which spasmophilia was excluded both by electrical reactions and biochemically and in which irreversible changes were found in the brain parenchyma. Burr (1922) also stressed the importance of tetany and felt that it was often overlooked as a cause of infantile convulsions.

The results of American workers upon the biochemical aspects of rickets and tetany (Howland and Marriot 1918, Howland and Kramer 1921, Kramer, Tisdall and Howland 1921) established on a surer footing the differentiation between tetany and other convulsive disorders. They found a low serum calcium in only two conditions, tetany and nephritis.

While the technique of calcium estimations by micro-methods was in its infancy Denis and Talbot (1921) published figures/

figures in which low calcium values were found in conditions manifesting no signs of tetany whatever such as acute infections and especially pneumonia. They also found high values including some in epilepsy. Their findings were contradicted by Kramer, Tisdall and Howland (1922). Gerstenberger and his associates (1923) published their findings in pneumonia and recorded a slightly reduced calcium in some cases. They also found that in 9 out of 10 cases the blood phosphorus was decidedly reduced in the absence of any signs of rickets.

Graham and Anderson (1924) described the biochemical findings in active and latent tetany. Active tetany was characterised by carpo-pedal spasm, laryngismus stridulus and convulsions; latent tetany by Chvostek's, Trousseau's and Erb's signs. The electrical sign of Erb however, they found of little value. In active tetany they found consistently low values for the serum calcium although there was no quantitative agreement between the degree of lowering and the degree of tetany manifest. In latent tetany the serum calcium was not always low. Powers (1925) found that the convulsions of whooping-cough were often hypocalcaemic especially between the ages of four and seventeen months.

Heuyer and Longchampt (1926) deride the German (sic) view that 90% of infantile convulsions are due to spasmophilia "dont l'existence clinique ne nous parait pas absolument demontrée". Not only in religious enquiries does/

does one find the "all-corroding, all-dissolving scepticism of the intellect!"

In a symposium upon convulsions in childhood, Graham (1932), Morris (1932) and Rennie (1932) each reported their investigations upon the various aspects of the problem. Graham limited his consideration to children under two years of age thereby excluding factors of aetiological importance in the adult. He was concerned with the special susceptibility of infants to convulsions and this he concluded was due to the spasmophilic diathesis. A calcium instability might be present without clinical evidence of rickets. In 500 cases under two years of age admitted over a period of five years, 123 had convulsions on the onset of their illness. From these were excluded cases in whom there was obvious intracranial disease. These, of which there were 39, formed a control series. The former group showed a marked seasonal incidence (Table II) which was very similar to that of tetany (Thiemich, 1906).

TABLE II

The Seasonal Incidence of Cases of Convulsions under Two Years of Age.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
123 cases	10	11	11	11	17	6	5	5	6	13	8	9
39 controls	2	5	2	4	1	4	2	5	2	6	6	4

Discussing the biochemical aspects Morris (1932) found a low/

low serum calcium frequently in these cases. He pointed out that the total calcium might be normal as in gastric tetany while the ionised fraction was reduced. Alkalosis and hyperphosphataemia would have this effect. Occasionally low values were found in cases without convulsions. Kennie (1932) found the total ionised calcium in the serum reduced in tetany while variations in the serum proteins affected only the bound calcium and had thus no effect upon neuromuscular excitability. He also found that the injection of amino-acids intravenously caused a definite fall in the serum calcium. Using a similar technique, Graham (1933) demonstrated the hypocalcaemic origin of convulsions in the first four months of life. These children had low values for serum calcium but the phosphorus was as a rule increased. In a discussion reported in the same paper Kramer agreed and quoted similar cases of his own; he believed that these showed the earliest manifestation of the biochemical upset of rickets.

In 1935 Morris, Ford and Graham continued the study of the pathogenesis of tetany. They found that a disturbance of acid-base balance and a retention of phosphate were the dominating factors only in so far as they might produce a fall in the blood calcium.

Frazer (1944) while attributing the convulsions of acute infections to an "exceptionally unstable nervous system" insisted upon the importance of rickets. "Whatever pulls the trigger, it is rickets which loads the gun." In 1942 Voigt provided/

provided evidence that tetany might lead to permanent damage of the brain. He studied a group of 103 children who had had tetany and took rachitic children as controls. Of the first group 45.6% were mentally defective. Löhr (1942) made contribution to the study of tetany in early infancy. He reviewed 7 cases in whom convulsions occurred in the second half of the first three months of life; clinical and radiological rickets were not the rule. Hyperexcitability on both mechanical and electrical stimulation were not always present together. Hypocalcaemia, hyperphosphataemia and a characteristic electrocardiogram were constant.

af Klercker (1932) raised the question of the diagnostic criteria of spasmophilia. He described cases in which the serum calcium was less than 7.5 mgm.% and yet the electrical reactions were normal. He also had cases in which there were the electrical reactions of tetany and yet the serum calcium levels were within normal limits. Siwe (1934) in a long and exhaustive paper also studied the problem of the diagnosis of tetany. In the results quoted the figure given for the phosphorus represents the total acid-soluble plasma phosphorus. In pure tetany he found the average serum calcium to be 7.3 mgm.% while the phosphorus was 6.12 mgm.%; the range of these figures however was extensive. The calcium varied from 5.8 to 11.5 mgm.% and the phosphorus from 4.9 to 12.0 mgm.%. In rickets with no radiological evidence of healing the serum calcium was 9.2 mgm.% (range 7.5 to 12.1 mgm.%) and the phosphorus/

phosphorus 4.6 mgm.% (range 2.4 to 7.3 mgm.%). The biochemical findings did not mirror the extent or the degree of the disease. He found no one finding constant in tetany and doubted the value of a single blood estimation.

Birk (1938) maintained the importance of spasmophilia in the aetiology of infantile convulsions and under this term included anything that would interfere with the calcium/phosphorus ratio such as alkalosis. He believed however that "Frühspasmophilie" of the newborn to be a misnomer and that the convulsions of this age were organic. He accepted Thiemich's "Späteklampsie" and denied any connection between tetany and epilepsy.

Horstmann and Petersen (1946) studied the incidence of tetany and rickets. They reviewed the cases of rickets and tetany diagnosed over a twelve year period 1924-35. After this time there had been a considerable drop in the incidence of these diseases. Their data comprised 1,259 cases of rickets and 478 of tetany. The seasonal incidence of rickets showed a rather flat curve with a maximum in February, March and April and a pronounced minimum in September. Tetany showed a sharp peak in March and a minimum from July to October. By observations upon the amount of sunlight they confirmed the correlation between the amount of sunlight and the amount of rickets and tetany.

Capper (1946) stated categorically that it was untrue to say/

say that the majority of children between the ages of six months and two years are spasmophilic. Personal observations on "numerous occasions" had failed to confirm tetany. Similarly he dismissed many reported cases of tetany of the newborn because a low calcium was not uncommon at that age and neither was a positive Chvostek's sign. In the first ten days of life he asserted that an infant normally showed a transient drop in the ionisable calcium of the blood. He demanded a positive Erb's reaction for the diagnosis of tetany and in this as in all else he is at variance with accepted opinion.

Guild (1948) wrote of the age incidence of tetany that 68% of her 293 cases occurred in the first year of life, 20% in the second and only 1.6% were over four years of age. Of the 199 cases occurring in the first year, 22 were in the second and third months of life and the peak was from six to nine months. With regard to seasonal incidence she found 70% of cases occurring in the first four months of the year with a sharp peak in March falling sharply after April and reaching its lowest incidence in July. She pointed out the importance of infection as a precipitating factor where tetany was latent and also that the convulsion of tetany was often unaccompanied by other signs of tetany.

EPILEPSY AND INFANTILE CONVULSIONS

Before continuing to discuss the voluminous literature upon the relation between infantile convulsions and epilepsy it is, I think, important to realise that the term "epilepsy" is used very differently by different authors. Those who discuss the prognosis of infantile convulsions use the term in its usual connotation of a chronic convulsive disorder with often a progressive mental deterioration as a sequel. The diagnosis of epilepsy in this sense spells tragedy for the parents and the term is not lightly used by the humane physician. It is obvious from the context that this is by no means what other writers intend. Authors who maintain the unity of all convulsive disorders do not imply this unhappy prognosis in every case of convulsions. On the contrary they inveigh against the Jeremiahs who hold this view. Manifestly this is a matter of definition. Those who hold that the basis of all convulsions is epileptic merely maintain that there is a fundamental unity in all convulsions however provoked, and that the spontaneous recurrent convulsions to which the term epilepsy is usually restricted, show a difference - great though it may be - that is a difference in degree and not of kind. Thus the term "symptomatic epilepsy" differs in no way from the term "symptomatic convulsions" except in so far as it is an "observation garnished with an assumption."

Aaron (1901) exemplifies this view when he calls "symptomatic/

"symptomatic epilepsy" the convulsion that he ascribes to the irritation of peripheral nerves by foreign bodies or cicatrices. His main thesis of the relationship between epilepsy and dyspepsia is rather nebulous and would appear to derive its authority equally from Galen and an increased output of indican.

Thiemich (1906) explicitly separates the convulsions of epilepsy, tetany and the convulsions of acute infections. "Alle krämpfe im Saüglingsalter, bei denen die spasmophile Grundlage ausgeschlossen werden kann, auch die ohne Übererregbarkeit auftretenden sogenannten "Fieberkrämpfe" und andere "Gelegenheitskrämpfe" im Sinne Hochsingers sind mit grosser Wahrschenlichkeit als epileptisch zu deuten." Thiemich and Birk (1907) investigated the outcome of 64 cases of infantile convulsions and found reaurrence in 11% of cases after two to four years but only a third were entirely free of nervous disorders. Birk (1909) pointed out how frequently epilepsy began in early childhood. Of his 70 cases, 52 began before the age of six years. Russell (1907) reported cases that were to demonstrate that epilepsy was due to sudden failure of the cerebral circulation but as none of his cases were epileptic he can hardly be said to have proved his point. Hutchison (1911) also believed that whereas infantile convulsions were not commonly followed by epilepsy they not infrequently showed neurological manifestations later. Alexander (1911) noted oedema of the pia arachnoid in epilepsy and/

and accordingly devised an operation of "fenestration" for which he claimed good results; it won no general acceptance. Still (1912) found a history of infantile convulsions in 20% of idiots. In his experience only a "very small proportion" of infantile convulsions progressed to epilepsy. Cruchet (1912) is also optimistic and wrote "qu'il existe des convulsions même répétées; qui guérissent, et qu'elles guérissent autant mieux que le sujet est plus jeune;" an observation at variance with most authorities.

Marchaud (1912) struck a warning note and claimed a connection between the convulsions of early infancy and later epilepsy. Guthrie (1913) contributed an inelegant metaphor when he likened the discharge of superfluous energy in idiopathic epilepsy to that of an automatic flush-cistern. He classed epilepsy as either symptomatic or idiopathic but went on to say that there must also be an inherent instability in the symptomatic group also.

Early in the century American workers were investigating the physiology of cerebral function at different levels of the brain (Stewart et alii, 1906, Stewart and Pike 1907, and Pike, Guthrie and Stewart 1908) and some of this work bore a direct relation to the aetiology of convulsions. This was followed up later by studies on epilepsy (Elsberg and Stookey, 1923 and Elsberg and Pike, 1926) on the same lines. The first point of interest arising out of their experiments was that convulsions could arise independently of the motor cortex. Furthermore, they/

they found that convulsions occurred during resuscitation from cerebral anaemia. On the return of the circulation from anything up to six hours after experimental occlusion of the cerebral circulation a generalised convulsion began and this in one experiment was accompanied by a weird "yowl".

Morse (1919) failed to establish any criteria of prognosis in infantile convulsions: "There is no way to determine immediately when a baby or a child has a convulsion, or has had repeated convulsions or repeated attacks suggesting petit mal, whether it has epilepsy or whether it will develop it later."

Morse (1922) criticised as much exaggerated the idea of reflex causes of convulsions. He had never seen a fit arising from dentition that could not be better explained in another way.

Burr (1922) investigated a large series of epileptics and found that in 15% there was a history of infantile convulsions followed by a remission of months or years.

An important paper was published by Patrick and Levy (1924) who compared a group of 500 epileptic children with a group of 752 unselected children. In the first there was a history of infantile convulsions in 20% while in the controls this was only 4%. There was a preponderant number of single early convulsions in the non-epileptic group (65% of the total) and moreover the majority (75%) of convulsions in this non-epileptic group were between six and seventeen months. They conclude that "Convulsions in infancy and childhood not epileptic, spasmophilic/

"spasmophilic or symptomatic of gross brain lesion are evidence of themselves of the indiviaual's increased chance of epilepsy." There is no "interval of safety" beyond which epilepsy will not occur. The more likely fore-runners of epilepsy are (1) those occurring before six months of age or later than eighteen months; (2) multiple convulsions; (3) severe convulsions; (4) localised convulsions; (5) those assigned to birth trauma; (6) those in which there is a family history of epilepsy or similar convulsions. The more fully these conditions are fulfilled the more likely is epilepsy to follow. The especially benign convulsions are the "teething spasms" of eleven to thirteen months.

In 1924 Thom (1924a) began an important survey which he has maintained until recent times. In his first series he records 111 cases who had convulsions before the age of four years. Of these, 62 had either died, become epileptic or mentally defective while 49 were well. Of 29 cases of spasmophilia 9 died, 2 became epileptic and 5 mentally defective. In a later series (Thom, 1924b) he found 7 to 10% of infantile convulsions in an unselected group of children. 29% of these were either retarded or epileptic but this rate was doubled where there was no obvious cause for the convulsion. In 101 cases of untreated rickets the incidence of convulsions was 4.27% while in 35 cases of treated rickets it was only 1.5%. He stressed the fact that infantile convulsions of all kinds including tetany might lead to damage to the brain and

that the prevention of infantile convulsions was therefore the prevention of epilepsy in later life.

Heuyer and Longchampt (1946) and Heuyer and Dublineau (1932) believe that symptomatic and idiopathic epilepsy are one and the same and that the cause of one is the cause of the other. Josephs (1926) claimed without much evidence that fasting was a cause of infantile convulsions even in the absence of a low blood sugar.

Brain (1926) investigated the hereditary factor in epilepsy. In 200 cases he found a family history of convulsions in 28% as opposed to probably under 10% in a control group of hospital patients. Onset in the first decade was more frequent in those with a family history. The proportion of first born was twice as high in the epileptics as that in the population from which they were drawn. He suggested a hereditary predisposition in at least 28% of cases.

In Collier's Lumleian Lectures in 1928 he states that "I shall attempt the argument that the clinical phenomena met with in idiopathic epilepsy, in epilepsy from local lesions of the brain, and in the symptomatic epilepsy occurring in disordered metabolic states, in general diseases and intoxications, are identical and truly indistinguishable. And that those occurring in narcolepsy, migraine, vasovagal attacks, idiopathic syncopal attacks, and perhaps also in tetany are phenomena of the same order and are closely allied to those of epilepsy with which they occasionally mix."

Epilepsy is common in birds and affects all mammals and in these occurs just as in man, in idiopathic and symptomatic form. Heredity has been demonstrated in pedigree cattle where epilepsy has apparently been transmitted with the finest characteristics of the stock. When discussing the convulsions of symptomatic epilepsy, namely those associated with acute infections in infancy, uraemia, eclampsia and tetany, he qualifies the distinction "premising on high authority that there is not one example of such convulsions which has not continued in some recorded case into established epilepsy." He is at one with Holmes (1927) in locating all epilepsy in the cerebral cortex.

Wyllie (1929) insists that "the epileptic fit is nothing else than a symptom; no such disease as epilepsy exists, or can possibly exist." Faerber (1929) believed that many cases of the so-called "Gelegenheitskrämpfe" did not have a good prognosis and were not infrequently followed by recurrent convulsions. Zappert (1932) from a review of the literature and a survey of his own material concluded that at least one third of all cases of epilepsy began before the age of ten years. He also made the important point that there was very little rise in the incidence of convulsions at school age and at puberty. He concluded therefore that the "times of stress" were not associated with an increased tendency to convulsions.

Kennedy (1931) when discussing the nature of the convulsive/

convulsive state first defined epilepsy as "a neural paroxysm in response to noxious stimulation." The wideness of his definition is manifest in his later statements. He went on to say that epilepsy was not a disease and that by giving the "epilepsy of pregnancy and uraemia" separate titles this fact is obscured. Of necessity he condemned the view of epilepsy as an incurable disease with inevitable progressive mental deterioration as needlessly lugubrious. His view of epilepsy though not necessarily correct is sufficiently important to warrant more extensive quotation.

"For the author's claim is nothing less than a qualitative unity and a quantitative difference in the various manifestations of epilepsy, from the major seizure through petit mal to migraine, to recurrent syncope and periodic endogenous emotional tempests." He elaborated his thesis of the unity of all convulsions in the use of the term "spectrum of epilepsy" in which there are many colours which may merge insensibly into each other. "The uraemia and eclampsia of pregnancy, the fits of general paralysis and brain tumour are there; the spasmophilic conditions of infancy are also to be thus grouped .... ; the chorea of pregnancy may be in this spectrum also; and, not very deep in the ultra-violet sector, are probably some cases of major hysteria ... ."

Hunt (1931) adduces evidence of two systems in the central nervous system just as there are in the autonomic system, one inhibitory and the other excitatory both normally working in harmony. Convulsions/

Convulsions could thus be the result of overactivity of the one or underactivity of the other. Clark (1931) adds the psychologist's contribution that a fit is simply (sic) a regressive and protective mechanism resorted to by an over-stressed organism and the various excitants are merely those which act upon the fundamental predisposition. However, of those that have fits only about 60% have the epileptic makeup and the rest are not true epilepsy.

Davenport (1931) on the ecology of epilepsy points out how widespread in nature is the convulsion. All races of men are susceptible but a large number of the animal kingdom also are known to have convulsions; the horse, cat, dog, ox, pig, rabbit and even birds like poultry and the canary. Obviously therefore factors peculiar to man cannot be aetiologically essential.

Thom (1931) discussed the relation between infantile convulsions and epilepsy of later life. Again the early beginning of epilepsy was stressed; of 300 epileptics half had fits before four years of age. He also reported the follow up of 109 cases of children who had convulsions before they were four years old and in whom the fits were not associated with any acute or chronic disease of the brain. He found evidence of brain damage in 57% of them.

Elsberg and Stookey (1931) summarised their experimental results. Convulsions were produced either by the injection/

injection of absinthe or by the release of clamps upon the innominate and left subclavian arteries. They found the susceptibility to convulsions reduced after a fit due to exhaustion. Susceptibility to absinthe was increased by thyroidectomy while diminished alkalinity of the blood had no effect; neither had starvation. Convulsions of arterial clamping could be prevented by an artificial saline cerebral circulation.

Swift (1931) described the presence of anomalous sinuses in the posterior fossa. Asymmetrical development of the transverse and sigmoid sinuses is common in epilepsy and the posterior fossa is commonly small. There is therefore a damming up of blood in the sinuses and an accumulation of cerebro-spinal fluid over the hemispheres and later dilatation of the ventricles. Operation to alleviate the congestion offered cure in 10% of cases and considerable improvement in 50%.

Gamble (1931) offered evidence of an underlying disturbance in body-fluid volume control in epilepsy but could not exclude its being merely the product of the convulsive state and therefore without pathogenic significance. Patterson (1931) after a review of the literature and of his own results concluded that the serum calcium in epilepsy was "normal within the quite wide limits of individual variation."

Oklon (1931) in an exhaustive study of the capillaries in epilepsy concluded that genuine epilepsy is not "endogenous" but "exogenous." The brain of the infant may during dystocia suffer/

suffer sufficient damage to give rise to capillary haemorrhages. These haemorrhages can be regarded as the starting point of the metabolic disturbance of epilepsy. The more protracted and pathological the labour, the more likely the damage. Smith (1930) published an investigation into the degree of intracranial damage to the child in labour. He found blood-stained cerebro-spinal fluid on cisternal puncture in 73.5% of cases. The possibility of contamination due to injury of vessels by the needles he excludes as it cleared in later taps. He therefore claims a "physiologic intracranial damage" incidental to labour.

McQuarrie (1926), McQuarrie, Husted and Manchester (1931) studied the effect of induced changes in the state of hydration in epileptic children. They found close relationship between the occurrence of seizures and the state of water balance. A negative water balance led to fewer convulsions while a positive balance led to more. This was confirmed by Fay (1931) who found that a proper control of fluid intake combined with dehydration produced in certain cases a diminished number of seizures. In both these papers very few cases were investigated and in fewer still were there positive findings.

Peterman (1932) attributed the higher incidence of convulsions in infancy merely to the incidence in that age period of certain diseases which produce convulsions; thus when the period of these diseases ceased, so did the convulsions. He entirely eliminated peripheral irritation as a cause of convulsions. Of/

Of 419 cases admitted with convulsions the following was the distribution of the diagnoses. These cases were all under fifteen years of age and formed 1.9% of the total admissions.

Epilepsy	144 cases or 34.4%
Acute infection	90 cases or 21.4%
Tetany	67 cases or 16%
Cerebral birth injury or residue	55 cases of 13.1%
Cause unknown	28 cases or 6.7%
Miscellaneous	35 cases or 8.4%

With regard to the mechanism or production of the convulsion of acute infections he stated that it might be either septicaemia or "dysregulation of the water balance which many infections produce (cerebral oedema)".

In 100 epileptic children Monrad (1932a) found the majority of cases beginning in the first year of life, a finding that does not seem to accord with his statement (Monrad 1932b) that the prognosis of infantile convulsions was better the younger the patient. Braun (1933) also believes many infantile convulsions to be epileptic and points out how early epilepsy often begins. In this connection he emphasises the importance of birth trauma as an aetiological factor. Lederer (1934) and Eckstein (1934a) also maintain this view. Gött (1935) classified all convulsions as epileptic further subdividing them according to whether they were symptomatic or epileptic. Faxèn (1935) followed up a series of/

of cases with convulsions. 15% of cases of epilepsy had remissions "d'une manière probablement durable." 3% of febrile convulsions were mentally retarded, 5% were epileptic and 6% had died. Clemmensen and Moltke (1934) recorded the age of onset of epilepsy and found 38% began before the age of three years.

Birk (1938) maintained that epilepsy was a distinct disease and deplored the indiscriminate use of the term for all kinds of convulsive disorders. Stauder (1939) however called all convulsions epileptic and emphasised the importance of unrecognised minimal birth trauma as a cause. He made an interesting addition to the concept of epilepsy as a merging series of convulsive states with idiopathic epilepsy and symptomatic epilepsy at its extremes. Many seeming symptomatic cases thereafter show progressive deterioration with spontaneous recurrence and epileptic character change. Such cases are intermediate in type and called by Stauder "Provoked epilepsy". He wrote: "Nicht die früheren Gelegenheitskrämpfe und nicht die physiologische Krampfbereitschaft des Kindesalters allein, bilden die Probleme der kindlichen Epilepsie, sondern diese provozierte Epilepsie, bei der sich Anlage und Umwelt zu wechselvollen und schwer einzureihenden Krankheitsverlaufen zusammenfinden." This underlying convulsive tendency in symptomatic epilepsy he regarded as hereditary. It was obviously meaningless to try and discern the number of epileptics that were/

were idiopathic and the number that were symptomatic when this was merely a matter of degree.

Fitch, Pigott and Weingrow (1938) and Pigot, Weingrow and Fitch (1939) found epilepsy to be most often demonstrably organic. The age of onset they found higher than other authors - the average age being 11.1 years.

Further animal experimentation to determine the mechanism of convulsions in acute infections was carried out by Wegman (1939). Kittens were subjected to a rapid rise in temperature; 25 out of 41 had convulsions. Adult cats subjected to the same treatment had convulsions in a much smaller proportion of cases; 2 out of 12. When the rise in temperature was made more gradually the incidence of convulsions was much less even though considerable heights were reached.

Peterman (1939) in an extensive review reiterates his opinions on the aetiology of convulsions and later (1940) offers a new classification in which idiopathic epilepsy is included as an organic cause. Price (1943) in a review of 224 cases of infantile convulsions found only 24 cases of epilepsy. Peterman writing again (1943) reviewed the position of electro-encephalography in the problem of convulsions and epilepsy. A positive electro-encephalogram (E.E.G.) had been obtained in 85% of clinically diagnosed cases of epilepsy, in 52% of non-epileptic relatives of epileptics and in 15% of controls. Abnormal E.E.Gs. were found in 50% of recruits who had a history of convulsions in infancy. All those who had an abnormal/

abnormal E.E.G. did not have convulsions and "How many potential epileptics live and die without ever experiencing a recognised convulsion only the electro-encephalograph can reveal to-day."

Thom (1942) continuing a survey begun in 1924 (page 52) believed that the old concept of epilepsy was discarded and that epilepsy was now regarded as a symptom of underlying pathology. A child might have one fit or many and then none until puberty. Moreover the relation might be more apparent than real. The same individual might have convulsions produced by different and independent factors at different ages. Of 5,403 consecutive admissions to a children's hospital, 1% were noted to have convulsions. He considered this too low and that some fits had been missed or ignored. Children's convulsions were still not taken seriously until a preventable degree of mental retardation appeared. Of 3,461 children who were a typical cross-section of the community, 233 had convulsions - 6.7%. These findings are summarised in Table III. He concluded that convulsions repeated over a period of weeks or months were more likely to be followed by epilepsy than one convulsion or a series of convulsions within a few days or hours. He emphasised that convulsions <u>per se</u> cause damage to the brain and mental retardation. In 8,000 unselected children 1% had epilepsy while in 395 children with a history of infantile convulsions 12% had epilepsy.

TABLE III

Incidence of Mental Defect and Chronic Convulsive Disorder Following Infantile Convulsions

Total children with convulsions	1927	1940
1 month to 5th year studied	265	130
Children continuing to have convulsions	35(13%)	13(10%)
Children defective	42(16%)	10(8%)
Children retarded	-	17(13%)

Buchanan (1946) also suggested the abolition of the old concept of epilepsy. Any brain given the necessary stimulus would react with a convulsion and children tended to be more susceptible. He put the percentage of children with infantile convulsions who ultimately become epileptic rather high, namely 15 - 20%. He made the point that the E.E.G. was not helpful under five years of age being very irregular and difficult to interpret.

The Aetiology and Changing Incidence of Convulsions in Childhood

Part II

THE AUTHOR'S INVESTIGATION

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

The present investigation was suggested by the fall in the incidence of rickets and tetany and by discussions on the aetiology of convulsions to-day arising out of that observation.

It was decided therefore to investigate the seasonal incidence of convulsions for three representative quinquennia of the quarter century 1922 - 1946: to confirm the seasonal incidence noted by Graham (1932, 1933) and to determine any subsequent change. At the same time additional information relevant to the wider problem of the nature of infantile convulsions could be extracted.

In order to complete the survey of this problem it was decided also to conduct a critical investigation both clinical and biochemical of all cases of convulsions admitted over a period of one year. It was thought that this would enable one to establish the extent to which demonstrable hypocalcaemia can be regarded as an aetiological factor in infantile convulsions to-day. It would also furnish an opportunity of comparing the findings in Glasgow with those in Sweden (Herlitz, 1941) and in America (Peterman 1932, 1939, 1940).

II - THE CHANGING INCIDENCE

PREAMBLE

From the foregoing review it is evident that there is much to be learned not only of the nature of convulsions in themselves, but of the relative importance of the various aetiological factors concerned. There is little unanimity in particular on the degree to which hypocalcaemia (to use a more precise term than either tetany or spasmophilia) can be implicated in infantile convulsions. One must remember, of course, when discussing the incidence of rickets and tetany, that this will vary considerably with the locality studied. It is certain, for example, that in Glasgow there has been in the past very much more rickets and tetany than in other cities with more sunshine and less poverty and overcrowding. Nevertheless, at the Royal Hospital for Sick Children one has noticed in recent years a marked falling off in the number of admissions of patients with rickets and tetany, and these diseases once so common are now comparatively rarely seen. This is in any case what one would expect with the gradual improvement in the standards of living and in particular with the fortification of National Dried Milk with vitamin D and the free supply of cod-liver oil in the Food Offices.

If, as was demonstrated clearly by Graham (1932, 1933), hypocalcaemia was the predominating cause of infantile convulsions in Glasgow and that this was manifested by a marked seasonal/

seasonal variation in incidence of these convulsions, then it is obvious that a general diminution of rickets and tetany would ipso facto not only reduce the number of hypocalcaemic convulsions but would likewise reduce the degree of seasonal variation and flatten the curve of monthly incidence. If the altering pattern of incidence of rickets and tetany were reflected in the incidence of infantile convulsions this would be a strong argument in favour of an aetiological connection. It would moreover go a long way towards meeting the criticisms of Herlitz (page 37) because the seasonal incidence of respiratory infections should not have changed the same way.

SCOPE OF INVESTIGATION

As records were available at the Royal Hospital for Sick Children, Yorkhill, Glasgow, it was decided to compare the incidence of convulsions in patients admitted to this hospital during three representative quinquennia, 1922-26, 1932-36 and 1942-46 respectively. Children are admitted to this hospital up to and including the age of twelve years. The material will then consist of all children in these periods who were admitted with a complaint of one or more convulsions or who subsequently had one or more convulsions during the period of stay in hospital. For the first period when the medical wards of this hospital were undivided, all medical admissions were included; for the next two, the admissions to one medical unit only were taken. As the number of medical beds/

beds in the twenties was less than in later years there is no very great disparity. The numbers of medical admissions for the three respective periods are 5,706, 3,769 and 4,884.

The standard of the case records in this hospital has been high at all times but nevertheless convulsions were not always noted on the front of the case-sheet under "complaint". Furthermore this in any case would not include those cases who developed convulsions later. It was accordingly decided that the only way to avoid gross inaccuracies was to scrutinise carefully each case-sheet. It was realised that the reading of over 14,000 case-sheets would of necessity be a laborious and time-consuming task but to be reasonably sure of one's figures was obviously essential. One cannot claim absolute accuracy, as apart from human error in compilation there is the possible error of omission in the case-records and of a number of lost case-records. These, I feel will be few and may be neglected. The problem of the criterion of diagnosis of a convulsion did not arise often. In the case of a generalised fit there was never any doubt on reading the history or the examination. In cases of "inward convulsions" the house physician sometimes recorded his indecision and in that case the internal evidence had to be assessed. If the mother appeared to be reasonably certain in the report that her child had had a sudden attack of unconsciousness the case was included. "Inward convulsions" are regarded as true convulsions on the authority of Still (1912) and/

and Graham (1932) and indeed on that of my own experience.

Each case was transferred to a Hollerith card and the following particulars noted and punched out according to a pre-arranged code. The child's name, sex and age headed the card. The age was then classified into one of eight groups. From birth to three months, over three months but under six months, over six months but under twelve months, over twelve months but under eighteen months, over eighteen months but under two years, over two years but under three years, over three years but under five years, and over five years. Although the precise date of birth was recorded in each instance these groups are convenient in assessing age-incidence. It was noted whether the child had had a convulsion previously. The type of convulsion was noted as either initial, continued or terminal. Initial convulsions were those occurring in the first twenty-four hours of the illness as far as this could be determined from the history. Terminal convulsions were those occurring in the last twenty-four hours of life. All the remainder were classed as continued. The degree of fever during the first twenty-four hours of admission was recorded as +, ++, or +++. A child was regarded as afebrile if the temperature was no higher than 100.4°F. A temperature of over this figure but under 102°F. was +; a temperature of over 102°F. but under 104°F. was ++ and a temperature of over 104°F. was +++. In practice the two middle categories (+ and ++) were/

were added together and the comparison made between the afebrile, the moderately fevered and the highly fevered (Plate XVI). All these temperatures are rectal. The presence or absence of acute infection was noted. Also the presence or absence of clinical rickets, craniotabes, clinical tetany, radiological evidence of rickets and the electrical reactions, if these were done, were recorded. Biochemical findings were also noted. The diagnosis and the outcome were recorded and the date of admission.

DISEASES ASSOCIATED WITH CONVULSIONS

During the three five-year periods there were 14,359 admissions and of these 1,225 had convulsions giving a percentage of total admissions of 8.53. Table IV gives the diagnoses of the causative diseases where these are known. Only cases with an obvious clinical epilepsy were so diagnosed; all other convulsions occurring without obvious associated disease were diagnosed convulsions of unknown aetiology. At this point it is convenient to differentiate between cases associated with obvious primary disease of the central nervous system and those which are not. The consensus of opinion allows us to include epilepsy among the former, but the convulsions of unknown aetiology must be included among the latter as containing presumably, a number of cases of tetany. Cases of frank tetany or cases in which biochemical analysis had/

TABLE IV

Diseases associated with convulsions

(I) Primary Disease of the Central Nervous System.	1922-26 Actual Figs.	1922-26 %age total	1932-36 Actual Figs.	1932-36 %age total	1942-46 Actual Figs.	1942-46 %age total
Epilepsy	50	11.0%	58	15.2%	60	15.4%
Inflammatory Disease	121	26.6%	50	13.1%	46	11.8%
Cerebral haemorrhage	2	0.4%	17	4.4%	9	2.3%
Mental Deficiency	27	5.9%	26	6.8%	53	13.6%
Miscellaneous	6	1.3%	4	1.1%	8	2.1%
Total	206	45.2%	155	40.6%	176	45.2%
(II) Without evidence of Primary Disease of the Central Nervous System.						
Respiratory System						
Acute Respiratory Disease	131	28.8%	83	21.8%	96	24.7%
Infectious Fevers	3	0.7%	6	1.6%	7	1.8%
Miscellaneous	1	0.2%	0	-	3	0.8%
Total	135	29.7%	89	23.4%	106	27.2%
Alimentary System						
Acute Infections	22	4.8%	46	12.0%	36	9.3%
Miscellaneous	2	0.4%	2	0.5%	3	0.8%
Total	24	5.2%	48	12.5%	39	10.1%
Urinary Tract						
Miscellaneous	12	2.6%	26	6.8%	8	2.1%
Miscellaneous						
Convulsions of unknown aetiology	44	9.7%	54	14.1%	48	12.3%
Tetany (without infection)	17	3.7%	8	2.1%	7	1.8%
Unclassified	16	3.9%	2	0.5%	5	1.3%
Total	77	17.3%	64	16.7%	60	13.4%
TOTAL	248	54.8%	227	59.4%	213	54.8%
Total All Cases	454		382		389	
Total Admissions	5,706		3,769		4,884	
Convulsions as percentage of total admissions.		7.95%		10.1%		7.9%

had revealed hypocalcaemia are only included as tetany if there is no associated infection; otherwise they are included under the heading of the associated disease. Each case is included only once and in cases with a double diagnosis the primary disease is taken with the proviso that it is with the convulsion that we are primarily concerned; accordingly where a pneumococcal meningitis supervenes upon a broncho-pneumonia and the convulsion is coincident with the appearance of the complication then the convulsion obviously belongs to the meningitic group.

It will be seen that the total figures are relatively constant for all three periods ranging between 7.9% and 10.1% of all admissions. Furthermore it is interesting to note that the proportions of cases classed as attributable to primary disease of the central nervous system remain much the same through all periods, the figures being 45.2%, 40.6% and 45.2% respectively.

The proportion of acute respiratory disease is much less than that found by Herlitz (1941) but he was dealing only with those convulsions that accompanied an acute infection. We could approximate more nearly to his figures if we exclude those cases for which no obvious cause, infective or otherwise, could be discerned, namely the convulsions of unknown aetiology; our figure would then be much higher. For example in 1922-26 there would be 131 cases in a total of 202 or 65%.

There/

There has been a fall in the incidence of inflammatory disease of the nervous system as might be expected. There are more cases of disease of the alimentary system associated with convulsions in recent periods but the figures are small.

MORTALITY

General:

Table V gives the mortality for all cases. Obviously the terminal convulsions must be excluded from any consideration of the mortality of convulsions. There has been a steady fall in the death rate which reflects the general therapeutic advance. The mortality of proved cases of tetany has fallen likewise.

TABLE V

Mortality of convulsions

	Total No. of cases	Total No. of deaths	Terminal convulsions	Deaths excluding terminal convulsions	Deaths excluding terminal convulsions as percentage of total number of cases
1922-26	248	98	33	65	26.2%
1932-36	227	76	32	44	19.4%
1942-46	213	42	24	18	8.5%
		Tetany			
1922-26	59	19			32.2%
1932-36	41	11			26.8%
1942-46	16	1			6.2%

Ileo-colitis:

Table VI gives the mortality for cases of ileo-colitis, most of which it may be assumed were cases of dysentery. In view of the frequent clinical experience of convulsions in severe cases of this disease I thought that it might be of interest to compare the mortality of ileo-colitis accompanied by convulsions with that of ileo-colitis without convulsions. There are no convenient records for the period 1922-26 which was therefore excluded from consideration. It will be seen that the case mortality for ileo-colitis with convulsions was 30.8% in 1932-36 while the mortality of all cases of ileo-colitis for this period was 23.9%. There has been a marked fall in the case mortality of ileo-colitis since then and for the period 1942-46 (since it so happened that none of the cases accompanied by convulsions were transferred to an infectious diseases hospital) a similar figure can be calculated and is found to be 14.3%. For the total case mortality of this period we can achieve only a rough approximation because too many were transferred and the outcome therefore is not known. If however, we regard all those transferred as cured, a most unlikely premiss, the case mortality would still be relatively high, 18.3%. In fact of course, it is likely to be higher. We can say therefore that this is the minimum case mortality and it is nevertheless higher than that for the cases accompanied by convulsions.

TABLE VI

Mortality of ileo-colitis

Ileo-colitis with convulsions					
	Total	Died	Transferred	Alive	Mortality
1932-36	13	4	-	9	30.8%
1942-46	7	1	-	6	14.3%
Ileo-colitis (including cases without convulsions)					
1932-36	88	21	-	67	23.9%
1942-46	60	11	37	12	(18.3%)

SEASONAL INCIDENCE

The main part of the analysis of these cases concerns the seasonal incidence and for this purpose all cases were tabulated according to the month of admission. In order to obtain figures of sufficient magnitude to be statistically significant the aggregate for each five-year period only can be used. There is no suggestion that cases attributable to primary disease of the central nervous system are associated with hypocalcaemia and these are tabulated separately and can to a certain extent be regarded as controls. In fact as will be seen later, controls will not be strictly necessary as we shall be concerned mainly with a comparison between the periods.

In 1922-26 there were 5,706 admissions to hospital and of these 206 had convulsions associated with primary disease of the central nervous system and 243 were admitted with convulsions associated with other diseases or of unknown aetiology. The/

TABLE VII

TABLE SHOWING SEASONAL DISTRIBUTION OF CASES OF CONVULSIONS ADMITTED DURING THE PERIOD 1922-1926

	Total Admissions	Convulsions associated with primary disease of the C.N.S.		Convulsions not associated with primary disease of the C.N.S. All ages		Under 5 yrs. of age	Under 3 yrs. of age.
	Actual figures	Actual figures	% each month's admissions	Actual figures	%	Actual figures	Actual figures
Jan.	567	17	3.0	33	5.8	31	29
Feb.	464	12	2.6	27	5.8	26	25
Mar.	446	13	2.9	28	6.3	27	24
Apr.	440	17	3.9	23	5.2	23	18
May	500	18	3.6	23	4.6	22	21
June	442	17	3.8	23	5.2	21	21
July	427	21	4.9	7	1.6	5	5
Aug.	494	23	4.7	15	3.0	15	14
Sep.	527	22	4.2	15	2.8	15	15
Oct.	532	15	2.8	22	4.1	20	17
Nov.	442	18	4.1	17	3.8	17	16
Dec.	425	13	3.1	15	3.5	13	12
Total	5706	206	3.6	248	4.3	235	217

The seasonal incidence of these cases is shown in Table VII. It will be noted that in disease of the nervous system there is no marked seasonal variation beyond a moderate rise in the summer months. This group of cases comprises a diverse number of diseases (Table IV) some of which have a seasonal incidence and therefore influence the seasonal variation of the whole according to their relative preponderance. Table X shows that it is not to the epilepsy group that this summer rise belongs. These results are shown graphically in Plate III. (There is no significant difference in these figures if they are calculated as a percentage of each month's admissions because the monthly admissions (Table VII) are fairly constant.)

Of the 248 cases with convulsions not attributable to primary disease of the central nervous system, 235 were under five years of age and 217 under three. There is no significant difference whether we take the total or the lower age groups; this may be due to the small figures (31 cases) over the age of three, or more likely due to the fact that the seasonal variation is a feature of the convulsions in the lower age group. This seasonal variation is however marked. There is a sharp fall in the summer months with a peak in January. If however we take, as we are entitled to do, the figures as a percentage of the monthly admissions, the peak is in March with the trough in July. These figures are shown in Table VII and/

and graphed in Plates I and II.

In 1932-36 there were 3,769 admissions to Dr. Graham's wards and of these 155 had convulsions due to primary disease of the nervous system (Table IV) and 227 convulsions in which there was no evidence of such disease. The seasonal incidence of these cases is shown in Table VIII.

The variation in the former group differs from that of the last five year period. Moreover there is a much greater difference between the actual figures and those calculated as a percentage of each month's admissions; it will be seen that each month's admissions are not so constant. Again however, this seasonal curve does not belong to the epilepsy group (Table X). It must be remembered, however, that here as in all three periods the number of epileptics is small. These figures are shown graphically in Plate III.

Of the 227 cases not attributable to primary disease of the nervous system, 216 were under five and 203 were under three years of age. Here again the number of older children is small (24 over three years old). In spite of the more marked monthly variation of admissions there is little difference between the actual figures and the figures expressed as a percentage of each month's admissions (Table VIII). As before also, there is little difference between the seasonal incidence in the lower age groups and the total. This seasonal incidence is still marked with a peak in March and

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TABLE VIII

TABLE SHOWING SEASONAL DISTRIBUTION OF CASES OF CONVULSIONS ADMITTED DURING THE PERIOD 1932-1936

	Total Admissions	Convulsions associated with primary disease of the C.N.S.		Convulsions not associated with primary disease of the C.N.S.			
				All ages		Under 5 yrs. of age	Under 3 yrs. of age
	Actual figures	Actual figures	% each month's admissions	Actual figures	%	Actual figures	Actual figures
Jan.	296	12	4.0	24	8.1	20	19
Feb.	294	15	5.1	18	6.1	16	16
Mar.	347	16	4.6	31	8.9	30	28
Apr.	309	18	5.8	24	7.8	23	21
May	332	16	4.8	25	7.5	24	23
June	295	17	5.8	13	5.8	13	13
July	275	17	6.2	13	4.7	13	12
Aug.	327	10	3.1	17	5.2	17	16
Sep.	329	10	3.1	18	5.5	17	15
Oct.	350	7	2.0	15	4.3	15	14
Nov.	312	9	2.9	13	4.2	12	12
Dec.	303	8	2.7	16	5.3	16	14
Total	3769	155	4.1	227	6.0	216	203

TABLE IX

TABLE SHOWING SEASONAL DISTRIBUTION OF CASES OF CONVULSIONS ADMITTED DURING THE PERIOD 1942-1946

	Total Admissions	Convulsions associated with primary disease of the C.N.S.		Convulsions not associated with primary disease of the C.N.S. All ages		Under 5 yrs. of age	Under 3 yrs. of age
	Actual figures	Actual figures	% each month's admissions	Actual figures	%	Actual figures	Actual figures
Jan.	540	18	3.2	16	3.0	15	15
Feb.	346	17	4.9	20	5.8	18	16
Mar.	425	20	4.7	20	4.7	20	20
Apr.	388	14	3.6	20	5.2	18	17
May	408	18	4.4	19	4.7	18	16
June	336	11	3.3	17	5.1	16	15
July	386	14	3.6	13	3.4	13	12
Aug.	463	16	3.5	20	4.3	19	18
Sep.	448	14	3.1	22	4.9	20	20
Oct.	387	13	3.4	13	3.4	13	12
Nov.	401	7	1.7	15	3.7	14	14
Dec.	356	14	3.9	18	3.9	17	17
Total	4884	176	3.6	213	4.4	201	192

a trough in June and July. The overall variation is however rather less; 13 as opposed to 26 in 1922-26. These results are shown graphically in Plates IV and V.

In 1942-46 there were 4,384 admissions to the same unit. Of these 176 had convulsions attributable to primary disease of the nervous system while 213 cases could not be so attributed. The seasonal incidence of these cases is shown in Table IX.

In those of primary neurological disease the seasonal variation has more in common with the last period having a fall in the summer. This is seen more especially when the figures are expressed as a percentage of each month's admissions. The high peak of admissions in January (540) distorts the curve slightly. The epileptic group (Table X) has a peak in February and March while the others oscillate more or less evenly. These figures are shown graphically in Plate III.

Of the 213 cases in which there was no evidence of primary disease of the nervous system, 201 were under five years of age and 192 under three. Here again the number of older children is small - 21 over the age of three years. As one would expect there is little difference between the seasonal incidence in the younger age groups and that of the total. (Plate VII). Calculation of the actual figures as a percentage of each month's admissions makes a slight difference to the shape of the curve (Plate VI). This curve however, shows a striking change from the former two periods. The range is only 9 and while there is

some/

some irregularity of curve almost all vestige of the former spring peak has gone.

TABLE X

Table showing seasonal distribution of convulsions due to epilepsy and other causes attributed to primary disease of the central nervous system.

	EPILEPSY			OTHERS		
	1922-26	1932-36	1942-46	1922-26	1932-36	1942-46
Jan.	3	4	6	14	8	12
Feb.	3	6	9	9	9	8
Mar.	5	5	8	8	11	12
Apr.	3	10	5	14	8	9
May	3	5	5	15	11	13
June	2	7	5	15	10	6
July	6	6	5	15	11	9
Aug.	6	2	4	17	8	12
Sep.	4	2	5	18	8	9
Oct.	4	4	4	11	3	9
Nov.	8	3	2	10	6	5
Dec.	3	4	2	10	4	12
Total	50	58	60	156	97	116

The incidence of tetany will be considered later but meanwhile it may be of interest to compare the seasonal incidence of the convulsions not associated with primary disease of the nervous system with that of tetany. In the three/

three five year periods there have been 116 unequivocal cases of tetany diagnosed on clinical, biochemical and in some cases electrical grounds. Of these, 88 were associated with an acute infection. The seasonal incidence is shown in Table XI and it will be seen that the peak is in March with a rapid fall in June.

TABLE XI

Seasonal Incidence of 116 Cases of Tetany

Jan:	20	Feb:	19	Mar:	27	Apr:	11
May:	14	June:	3	Jul:	4	Aug:	3
Sep:	1	Oct:	7	Nov:	6	Dec:	1

Statistical Comment: I am grateful to Dr. R.A. Robb of the Mathematical Department, University of Glasgow for the following statistical comment.

"If we consider the number of cases of convulsions in any one month in proportion to the population of children exposed to risk we can at once say that the probability of convulsions is very small and the numbers of convulsions for the various months may thus be treated/

treated as coming from a Poisson population.

Owing to the number of days in each month being unequal we should first correct the original data by adjusting them proportionately, e.g.

No. of days in 5 years.	January 165	February 141

Thus the February figures should be increased in the ratio $\frac{165}{141}$. The adjusted data for the period 1922-26 assuming 31 days for each month are

33: 31.6: 28: 25.3: 23: 25.3:
7: 15: 16.5: 22: 18.7: 15: Total 260.4

The corrections, however, are small and only slightly affect the results: the original data have thus been used in the following analysis.

We test the hypothesis that the number of cases of convulsions for the various months is homogeneous, that is, show no significant variation from each other, by calculating the Poisson Index of Dispersion, namely

$$\chi = \sum_{i=1}^{12} \frac{(x_i - \bar{x})^2}{\bar{x}}$$

where x_1 is the number of deaths in January

x_2 " " " " " " February

. . .

. . .

x_{12} " " " " " " December

and $\bar{x} = \frac{x_1 + x_2 \text{ ---- } + x_{12}}{12}$

There/

There are 11 degrees of freedom and if $\chi^2 > 19.7$ we may say that there is a significant seasonal variation.

The following results were obtained:

Period	χ^2	Remarks
1922-26	27.1	Highly significant
1932-36	19.5	Bordering on significance
1942-46	5.4	Not significant

(It should be remarked however, that there appears to be a slight tendency for the number of cases to fall as one proceeds from 1922-26 to 1942-46. This variation will appear in the calculations for χ^2 and make them slightly higher than they should be. See also note below regarding the significance to the totals for each period.)

Thus there is a marked seasonal variation in 1922-26 and a tendency for such in 1932-36. The figures for the period 1942-46 however show variations which must be considered as random fluctuations.

By a well known property of Poisson distributions the totals for each period, viz.

Period	No. of cases
1922-26	248
1932-36	227
1942-46	213

are also Poisson, and a χ^2-test applied as shown above shows that there is <u>no</u> significant variation between the/

the totals.

In order to investigate whether the number of cases for each month for all the periods are in a homogeneous group, I have applied a χ^2-test which in effect amounts to investigating whether for any one month the numbers of cases for each period are merely proportional to the totals for each period. For example

	January	Whole Year
1922-26	33	248
1932-36	24	227
1942-46	16	213

Is it the case that the ratio of 33 to 24 to 16 is apart from random fluctuations the same as the ratio of 248 to 227 to 213? and similarly for the other months. We find for 22 degrees of freedom

$$\chi^2 = 19.454, \quad .70 < P < .50$$

For significance the value of χ^2 should be a value, χ^2_0, say such that the probability of P of values of $\chi^2 > \chi^2_0$ should be 0.05 or less. Here P lies between 0.70 and 0.50 and thus we say that the data are homogeneous.

This result might appear to be contrary to that obtained above, namely that the period 1922-26 shows a significant seasonal variation whereas the period 1942-46 shows no significant variation. This may be explained by saying/

saying that while the fluctuations in 1922-26 are sufficiently violent to cause significant variation and those in 1942-46 are rather small causing no significant variation, the fluctuations in 1922-26 from month to month keep in step with those in 1942-46 to a degree sufficient to make differences between them non-significant. To illustrate these particular periods I have adjusted the monthly data for the period 1942-46 so that the total number of cases in that period is equal to the total number in 1922-26. It will be seen from the diagram (Plate XIX) that there is a tendency for the adjusted 1942-46 numbers to keep in step with those for 1922-26 and the differences taken as a whole cannot be considered significant. (Using the original data I have tested the hypothesis that for any one month the ratio of the number of cases in 1922-26 to the number of cases in 1942-46 is equal to the ratio of the total number of cases in these periods, viz. $\frac{243}{213}$ apart from random fluctuations, and I find $X^2 = 13.7$, $.30 < P < .20$. This shows that the data should be considered homogeneous.)

The final conclusions are that the monthly variations for 1922-26 are sufficiently large to give a marked seasonal variation. The variations for 1932-36 are smaller and border on significance, while those for 1942-46 are small and cannot be considered significant. The monthly variations for each period keep in step to a certain extent, however, and/

and the whole series of data must be considered homogeneous."

AGE INCIDENCE

The age incidence of all periods and also of the 116 cases of tetany is shown in Table XII.

Cases of Primary Disease of Nervous System.

In 1922-26 56 of the 206 cases were under one year of age and 108 were under two years of age. 60 were in the tetany age-group of six to eighteen months. Of the first two years of age, twelve to eighteen months contained the peak but 77 cases were over three years old. This is shown graphically in Plate VIII.

In 1932-36 51 cases out of the total of 155 were under one year of age while 72 were under two years of age. In the tetany age-group of six to eighteen months there were 30 cases. Of the first two years the peak was in the first three months with a decided minimum in the age group eighteen to twenty-four months. 67 cases were over three years old. This is shown graphically in Plate X.

In 1942-46 62 out of the total of 176 cases were under one year of age and 79 were under two years of age. In the tetany age-group of six to eighteen months there were 32 cases. Of the first two years the maximum incidence was again in the first three months of life with a minimum in the age group twelve to eighteen months and eighteen to twenty-four months.

74 cases/

TABLE XII

AGE INCIDENCE OF CONVULSIONS IN THREE FIVE YEAR PERIODS

	Convulsions attributed to primary disease of the C.N.S.			Convulsions not attributed to primary disease of the C.N.S.			
	1922 to 1926	1932 to 1936	1942 to 1946	1922 to 1926	1932 to 1936	1942 to 1942	Tetany 116 cases
Birth to 3/12	11	22	25	38	58	48	17
Over 3/12 & under 6/12	18	11	13	41	36	26	28
Over 6/12 & under 12/12	27	18	24	57	50	26	32
Over 12/12 & under 18/12	33	12	8	45	19	27	24
Over 18/12 & under 2 yrs.	19	9	9	21	19	21	8
Over 2 yrs. & under 3 yrs.	21	16	23	23	21	31	3
Over 3 yrs. & under 5 yrs.	27	28	28	10	13	22	1
Over 5 yrs.	50	39	46	13	11	12	3
Total	206	155	176	248	227	213	116

74 cases were over three years of age. This is shown graphically in Plate XII.

Cases Not Attributed to Disease of Nervous System.

In 1922-26 136 out of the total of 248 cases were under one year of age and 202 cases were under two years of age. 102 cases were in the age-group six to eighteen months. Of the first two years there is a marked peak incidence in the second six months of life and a figure not much less in the third six months of life. Only 23 cases were over three years of age. This is shown graphically in Plate IX.

In 1932-36 144 out of a total of 227 cases were under one year of age and 182 were under two. In the age group six to eighteen months there were 69 cases. In the first two years of life the peak incidence is this time in the first three months but the figure for the age-group six to twelve months is not much lower. There is a sudden fall after the first year of life and only 24 cases are over three years of age. This is shown graphically in Plate XI.

In 1942-46 100 cases out of the total of 213 were under one year of age and 148 cases were under two. In the age-group six to eighteen months there were 53 cases. In the first two years of life there is a marked peak incidence in the first three months of life while the incidence in the other age-groups remains relatively steady with a falling off in the older groups. There are only 34 cases over the age of three years. This/

This is shown graphically in Plate XIII.

Tetany.

The age incidence of the 116 cases of tetany taken from all three five year periods is shown graphically in Plate XIV. There are 77 cases under one year and 109 cases under two years of age. The largest number of cases falls within three and eighteen months (34 cases) but there is a significant incidence in the first three months of life (17 cases).

DISTRIBUTION OF TYPES OF CONVULSIONS

The distribution of types of convulsions, either initial, continued or terminal, of all periods together with that of the 116 cases of tetany is shown in Table XIII.

Cases of Primary Disease of Nervous System.

In 1922-26 73.3% of cases had convulsions that were continued beyond the first 24 hours of the illness and were not terminal. In 1932-36 this figure was 67.1% and in 1942.46 it was 71.5%. The numbers of terminal convulsions for the three periods respectively were 15.1%, 9.0% and 4.7%. The number of initial convulsions 11,6%, 23.9% and 23.8%. This is shown in a compound histogram in Plate XV.

Cases Not Attributed to Disease of Nervous System.

Here there is seen a steady rise in the proportion of initial convulsions from 1922-26 to 1942-46, the respective figures/

TABLE XIII

DISTRIBUTION OF INITIAL, CONTINUED AND TERMINAL CONVULSIONS

		1922-26		1932-36		1942-46	
		Actual figures	%	Actual figures	%	Actual figures	%
Convulsions associated with primary disease of the C.N.S.	Initial	24	11.6	37	23.9	42	23.8
	Continued	151	73.3	104	67.1	126	71.5
	Terminal	31	15.1	14	9.0	8	4.7
Convulsions not associated with primary disease of the C.N.S.	Initial	95	38.3	98	43.2	122	57.3
	Continued	120	48.4	96	42.3	67	31.5
	Terminal	33	13.3	33	14.5	24	11.2
Tetany - 116 cases	Initial	40	34.5				
	Continued	75	64.6				
	Terminal	1	0.9				

figures being 38.2%, 43.2% and 57.3%. This rise has been at the expense of continued convulsions which have accordingly fallen from 48.4% through 42.3% to 31.5%. The terminal convulsions have remained relatively constant being 13.3% in the first period, 14.5% in the second and 11.2% in the third. These are shown graphically in a compound histogram (Plate XV).

Tetany.

The predominating type of convulsions in tetany is the continued convulsion being 64.6% of the total. Terminal convulsions are only rarely tetanic (0.9%). A histogram of these figures is also given in Plate XV.

DEGREE OF FEVER ON ADMISSION

Only those cases with convulsions not attributable to primary disease of the central nervous system were considered and of these only those with evidence of an acute infection (Table XIV). The total number of cases concerned was 170 in the first period, 160 in the second and 148 in the last. Of these 14.8% were afebrile while 32.9% had a temperature of over 104°F in the period 1922-26. In the second period 19.5% were afebrile while 23.7% had a temperature of over 104°F. In the period 1942-46, 30.3% were afebrile while only 16.2% had a temperature of over 104°F. This is shown graphically in Plate XVI

In tetany where only those with an acute infection were selected, of a total of 88 cases, 20 were afebrile and 11 had

a/

TABLE XIV

DEGREE OF FEVER ON ADMISSION IN CASES OF CONVULSIONS ASSOCIATED WITH AN ACUTE INFECTION BUT NOT ATTRIBUTED TO PRIMARY DISEASE OF THE NERVOUS SYSTEM

	1922-26			1932-36			1942-46			88 cases of Tetany with an acute infection
	Actual figures	%		Actual figures	%		Actual figures	%		
100.4°F or below	25	14.8		31	19.5		45	30.3		20
Over 100.4°F Under 102°F	33	19.4	52.3	42	26.2	56.8	31	21.0	53.5	
Over 102°F Under 104°F	56	32.9		49	30.6		48	32.5		57
Over 104°F	56	32.9		38	23.7		24	16.2		11
Total	170			160			148			88

a temperature of over 104°F.

HISTORY OF PREVIOUS CONVULSIONS

Table XV shows the number of cases with a history of previous convulsions. In diseases of the central nervous system there is a marked rise in the number with such a history from 27% in 1922-26 to 47.7% in 1932-36 and 48.8% in 1942-46. In cases not attributable to primary disease of the central nervous system there has been little change. In 1922-26 the figure was 15.7%, in 1932-36, 22.5% and in 1942-46 it was 17.8%.

TABLE XV

Table showing the number of cases with a history of previous convulsions

	1922-26 Actual figures	%	1932-36 Actual figures	%	1942-46 Actual figures	%
Convulsions associated with primary disease of the C.N.S.	56	27	74	47.7	86	48.8
Convulsions not associated with primary disease of the C.N.S.	39	15.7	51	22.5	38	17.8

THE INCIDENCE OF CLINICAL RICKETS AND TETANY

In view of the rarity of both these conditions to-day it would/

would be surprising if there had not been a marked reduction in the number of cases of convulsions showing at the same time clinical evidence of these diseases. (Table XVI).

TABLE XVI

The incidence of clinical rickets and clinical tetany in cases of convulsions during three five year periods

	Rickets			Tetany		
	1922 -26	1932 -36	1942 -46	1922 -26	1932 -36	1942 -46
Convulsions attributed to primary disease of the C.N.S.	25	5	2	0	1	0
Convulsions associated with an acute infection and not attributed to primary disease of the C.N.S.	88	48	22	56	25	1
Convulsions not associated with an acute infection and not attributed to primary disease of the C.N.S.	16	6	1	16	2	0
Total convulsions not attributed to primary disease of the C.N.S.	104	54	23	72	27	1

Cases of Primary Diseases of Nervous System.

In 1922-26 there were 25 cases of clinical rickets and no cases of clinical tetany. In the next two periods there were 5 and 2 cases of clinical rickets respectively while there was/

was one case of clinical tetany in 1932-36 and none in 1942-46. The incidence of clinical rickets is shown graphically in Plate XVII and that of clinical tetany in Plate XVIII.

Cases Not Attributed to Disease of Nervous System.

These were divided into those associated with an acute infection and those that were not. Of the former there were 88 cases of rickets in the first period and only 22 in the last. The figures for tetany are even more striking with 56 cases in the first period and only 1 in the last. The totals are 104 cases of rickets in 1922-26 and 23 in 1942-46 while those for tetany are 72 and 1 respectively. These are shown graphically - rickets in Plate XVII and tetany in Plate XVIII.

III - D I S C U S S I O N

DISEASES ASSOCIATED WITH CONVULSIONS

One must beware of drawing conclusions from the number of admissions to a hospital. Many factors besides the actual incidence of the disease determine the number of cases admitted to a hospital at one time. Urgent and serious cases will often be admitted in much higher proportions than the general incidence would suggest. Furthermore should the capacity of a hospital be reduced the reduction of urgent admissions will be very much less than that of routine or non-urgent admissions. This of course applies particularly to convulsions.

During the last twenty-five years the numbers of cases of convulsions admitted have been considerably increased. In Table IV the figures for the two later five year periods represent approximately half the admissions to the hospital. Thus the estimated number of convulsions admitted during the three periods would be, 1922-26, 454, 1932-36, 764, and 1942-46, 778. We are not entitled on this account to assume without further evidence that there has been an increase in the absolute incidence of convulsions in Glasgow. It may well be that the expansion in the size of the hospital together perhaps with a change in the policy of the local practitioners will suffice to explain the apparent increase. On the other hand there/

there is nothing in this finding to preclude the possibility that there has been an increase in the incidence of convulsions in this area though should this be the case one might rather expect the convulsions expressed as a percentage of total admissions to increase. For the three five year periods this would be 7.95, 10.1 and 7.9 respectively. As we shall see later the figure for 1947/48 is rather less, 6.0%. This illustrates the point that whereas we may not draw conclusions from the total numbers of admissions we may from their proportional relationships. More particularly when we are considering a symptom such as a convulsion we may examine the relative proportions of the various causative factors.

On examining Table IV one notices that there has been no change in the relative proportions of cases attributable to primary disease of the central nervous system and cases not so attributable. The three figures 45.2%, 40.6% and 45.2% are sufficiently close to indicate no significant change. This is the more remarkable when we note that there has been a marked fall in the incidence of acute inflammatory disease of the central nervous system. This fall incidentally is largely that of meningitis, both meningococcal and tuberculous. The proportion due to inflammatory disease has fallen to less than half during the twenty-five years under consideration. This I think we may take to be a true fall in the incidence of the causative disease rather than a fall in the incidence of convulsions in these particular diseases. The increase that counteracts/

counteracts this fall in the total percentage is largely in the group of epilepsy and mental deficiency. It is of course possible that more of these are now being sent to hospital though it is difficult to see why this should be so. One is tempted to the conclusion that there has been a definite increase in both these diseases in the last twenty-five years. That this is not unlikely is suggested by the two last surveys of the number of mental defectives in England and Wales, one by a Royal Commission in 1904 and the other by the Mental Deficiency Committee in 1924. The latter found the incidence almost double that of the former (Tredgold, 1937) and as this included an increase in the number of cases of gross defect this cannot be explained on the basis of more care in the later survey. Although these surveys are not contemporary with the period of present consideration they suggest the possibility of an increase in the amount of mental deficiency dependent presumably upon genetic factors.

It is however with those convulsions that are not attributable to primary disease of the central nervous system that we are primarily concerned and the corollary that there has been no change in the relative incidence of these either is surprising in view of the other findings. We know that the number of cases of undoubted tetany has fallen from 59 in 1922-26 to 16 in 1942-46 (Table V) and yet the proportion of the total admissions that had convulsions due to/

to conditions other than primary disease of the central nervous system is exactly the same, 54.8% for both periods. The reason is not to be found in the other causative diseases as reference to Table IV will show that all variations are too small to be regarded as of any importance even in the aggregate. Nevertheless if we accept as we must, that there has been a marked fall in the incidence of frank tetany at least, there must have been a corresponding increase in another aetiological factor still mainly associated with the general systemic infections. We shall return to this question later when we come to speculate upon the nature of the convulsive state.

The other point of importance that arises out of this table is the type of illness that is associated with convulsions. Herlitz (1941), as we have been, found that acute pharyngeal infections accounted for nearly 80% of his cases. I think that we may discount the minute localisation of this diagnosis and assume that they are what we would term cases of upper respiratory infection. Using the same criteria in our series we find 65% of cases associated with acute respiratory disease. The difference is possibly one of selection. In both series one is struck by the smallness of the number of cases of acute gastro-intestinal disease associated with convulsions. This is in spite of the very great prevalence of such diseases which until recently rivalled acute respiratory disease as a killing factor in infancy. If Table IV is read in conjunction with Table VI/

Table VI it will be seen that of the 46 cases of acute infections of the alimentary tract in 1932-36, 13 were cases of ileo-colitis or dysentery. There were however only 88 cases of ileo-colitis admitted during this period and it is obvious that this disease is accompanied by convulsions in this hospital much more often than is gastro-enteritis of which there were 422 cases admitted during the same period. That is to say that there were 13 cases of ileo-colitis with convulsions out of a total of 88 giving a convulsion rate of 14.6% while there were only 33 cases of acute gastro-enteritis with convulsions out of a total of 422 giving a convulsion rate of only 7.8%. One may note in passing that acute ileo-colitis is invariably accompanied by some degree of fever which is often high whereas acute gastro-enteritis is more often afebrile or accompanied by only slight fever. One might argue that the milder cases of ileo-colitis are diagnosed as clinical dysentery by the appearance of blood and mucus in the stools and accordingly sent to an Infectious Diseases Hospital while those cases that are ushered in with a convulsion are usually sent in to the general hospital on that account before the appearance of the characteristic stools. I shall consider later whether the cases of ileo-colitis accompanied by convulsions are more grave than those that are not.

MORTALITY

Little more than the statement of the facts need be said/

said of the general mortality of convulsions. The striking fall is presumably merely a reflection of the increased therapeutic efficiency of the last quarter century. The fall from 26.2% to 8.5% is mirrored by the fall in the number of deaths from pneumonia reported by the Medical Officer of Health for Glasgow in the same three periods (Table XVII).

TABLE XVII

Deaths from Pneumonia in various years as published by the Medical Officer of Health for the City of Glasgow

Year	No. of Deaths	Year	No. of Deaths	Year	No. of Deaths
1922	2,303	1932	1,917	1942	731
1923	1,400	1933	1,346	1943	840
1924	2,198	1934	1,619	1944	696
1925	1,665	1935	1,516	1945	529
1926	1,758	1936	1,596	1946	661

The same trend can be seen in the deaths under one year of age due to respiratory disease from the same source (Table XVIII). It will be seen that the mortality in tetany has shown an even greater fall. The fall in mortality can in no/

no sense be attributed therefore to the relative absence in later years of the factor of tetany which one would expect to influence the prognosis unfavourably.

TABLE XVIII

Deaths under one year of age due to diseases of the Respiratory System as published by the Medical Officer of Health for the City of Glasgow

Year	No. of Deaths	Year	No. of Deaths	Year	No. of Deaths
1922	631	1932	820	1942	...
1923	...	1933	489	1943	357
1924	368	1934	648	1944	317
1925	642	1935	528	1945	188
1926	625	1936	593	1946	277

Ileo-colitis.

It is common clinical experience in paediatrics to meet the acutely ill child who is admitted into hospital with convulsions and who dies shortly thereafter without manifesting any of the signs of the acute ileo-colitis that is revealed post mortem. It might be interesting therefore to determine if possible what effect upon the prognosis a convulsion would have in acute ileo-colitis. Unfortunately all the necessary data were not readily available and the transfer of cases of proved dysentery in later years complicated the issue. At all events the figures are small but/

but one may permit oneself the tentative conclusion that a convulsion does not of itself affect the prognosis adversely.

SEASONAL INCIDENCE

Cases of Primary Disease of Nervous System.

The seasonal incidence of meningococcal meningitis and of tuberculous meningitis, of encephalitis, anterior poliomyelitis and possibly of benign lymphocytic chorio-meningitis all will contribute to the curve of seasonal incidence in proportions dependent upon their relative incidence. That being so, the seasonal incidence makes a rather unsatisfactory control series for the others. In my series they seem to be more variable than in Graham's (1932) and are therefore less satisfactory. Nevertheless one may feel fairly sure that in spite of the smallness of the numbers, there is nothing inherent in idiopathic epilepsy that would give a seasonal curve; nothing in fact peculiar to the convulsive state per se. That being so we can turn to the study of the seasonal incidence of the other group.

Cases Not Attributable to Disease of Nervous System.

We have seen that there is a marked curve of seasonal incidence of these cases in 1922-26 and that this is less marked but of the same form in 1932-36 while it has for all practical purposes disappeared by 1942-46. When we take into consideration

consideration the statistical comment and compare the curve for 1922-26 with that of the adjusted curve for 1942-46 it is obvious that there has been a considerable change in the pattern of incidence. It is in this connection not surprising that the whole series of curves should be considered homogeneous and the difference may to some extent be regarded as one of degree rather than of kind. Plate XIX shows these two curves and in addition it shows the seasonal incidence of our cases of tetany. This latter curve differs in no essential from those reported by Thiemich (1906), Horstmann and Petersen (1946) and Guild (1948). On comparing the three curves it will be seen that the curve for 1922-26 approximates more nearly to the shape of the curve of tetany while that of 1942-46 differs markedly. The picture in fact of the first period and that of 1932-36 is in complete agreement with the findings of Graham (1932, 1933) and accords well with his thesis that the main part of these convulsions are in fact hypocalcaemic and show the same seasonal incidence as tetany. Moreover a comparison between the three curves shows a state of affairs perfectly compatible with the gradual diminution of tetany as an aetiological factor and a corresponding flattening out of the curve of seasonal variation. The curve for 1942-46 will therefore show a variation dependent upon the combined effect of any remaining cases of hypocalcaemia together with that of the seasonal variation of the causative diseases.

This/

This brings us to the pertinent criticism of Herlitz (1941) who denies the significance attributed by Graham (1932) to the seasonal variation of initial-fever convulsions. He makes the point that this seasonal variation is not due to any spasmophilic associations but is only the usual seasonal incidence of respiratory infections which in his series are an almost invariable accompaniment. This is at first sight a formidable criticism that must be met before any conclusions whatsoever can be drawn from the variation in seasonal incidence. His argument appears to me to premise a fallacy and its invalidity can be demonstrated fairly easily.

In the first place there is implicit in his argument that the seasonal incidence of respiratory disease is identical with that of Graham's and my series of convulsions and with that of tetany. This however is not so. In our series of cases of tetany the seasonal incidence is in complete agreement with those cited by other authors (Thiemich, 1906, Horstmann and Petersen 1946, and Guild 1948) who find that there is a distinct peak of incidence in March. Furthermore Horstmann and Petersen make the point that whereas in rickets the curve has a rather broad peak straddling some months, that of tetany has a sharp peak confined to March. This is by no means what one finds in respiratory disease. Nevertheless it is difficult to find figures for comparison to confirm this point. It is interesting however to note the seasonal variation of the notifications/

notifications of acute primary pneumonia in the City of Glasgow for two representative years (Table XIX).

TABLE XIX

Seasonal Variation of Cases Notified as Acute Primary Pneumonia in the City of Glasgow in the Years 1936 and 1946. (M.O.H. Reports)

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec
1936	895	482	435	407	387	352	212	210	266	553	851	717
1946	1112	763	703	410	415	298	274	208	226	390	640	712

These figures confirm if confirmation were necessary, that pneumonia is a winter and not a spring disease. One may also, I think, assume that the other acute respiratory diseases have much the same seasonal variation. That being so, it is not an explanation of the seasonal variation to say that it is to be attributed to the causative disease.

Even if this were so one would have to explain the disappearance of this seasonal variation in the period 1942-46. One may say that there has been a falling off in the number of cases of acute respiratory disease or that modern treatment prevents their becoming serious enough to provoke a convulsion. Neither of these hypotheses will bear examination. In the first place while the proportion of acute respiratory disease in our series is less than in that of Herlitz (1941) it is nevertheless quite/

quite large and in addition remains more or less constant during all three periods. In other words acute respiratory disease is just as common an associate of convulsions in 1942-46 as it was in 1922-26 and if it were responsible for the seasonal variation in the latter period it should produce it in the former as well. One can examine further the suggestion that the incidence of acute respiratory disease has fallen in the last twenty-five years. Table XX shows the number of cases of acute primary pneumonia notified in Glasgow during the three five year periods. These figures are not very reliable as the distinction between acute primary pneumonia and the secondary variety is of necessity arbitrary and the criteria variable in the extreme. Nevertheless they may be taken as an indication of the prevalence of pneumonia and it is obvious that there has been no downward trend whatever. The deaths under one year from diseases of the respiratory system are shown in Table XVIII and these, as would be expected, show a downward trend following the infantile mortality. This must be attributed to treatment and is not likely to be dependent upon a fall in incidence.

TABLE XX/

TABLE XX

Number of Cases of Acute Primary Pneumonia Notified in the City of Glasgow as Published by the Medical Officer of Health

Year	No. of Cases	Year	No. of Cases	Year	No. of Cases
1922	5,967	1932	7,555	1942	6,151
1923	4,346	1933	5,194	1943	4,876
1924	6,747	1934	6,754	1944	5,680
1925	5,802	1935	6,171	1945	6,728
1926	.....	1936	6,035	1946	5,270

The efficacy or otherwise of therapy in acute disease cannot be said to influence the incidence of convulsions as it is at the beginning of the illness that the convulsion typically occurs. Moreover a convulsion is not a manifestation of the severity of the illness. It does not for example, denote the onset of a pneumonia in a case of acute bronchitis; a development that might be prevented by chemotherapy. It is in fact more likely to come at the beginning of the initial upper respiratory infection. This does not of course, refer to the convulsion that ushers in a complication such as meningitis nor to the agonal convulsions of the dying.

We cannot escape the conclusion that incidental or febrile convulsions, "Gelegenheitskrämpfe," or call them what we will, had a marked seasonal incidence twenty-five years ago and that this incidence followed closely that of tetany but resembled/

resembled not at all that of the major causative diseases. Furthermore that this seasonal variation has disappeared almost entirely while the total incidence has nevertheless remained constant. That this indicates that the major factor in the aetiology of infantile convulsions in Glasgow was hypocalcaemia until the late thirties at least, there can be no reasonable doubt. The only discrepant finding is the constant incidence of the convulsion unassociated with primary disease of the central nervous system. This suggests that the hypocalcaemic convulsion has been replaced by another. Other findings seem to confirm this suggestion which will be taken up again later.

AGE INCIDENCE

The Plates VIII and XIV which show graphically the age incidence of the two main groups of convulsions for each five year period are irregular histograms. The age intervals are not equal and each column is not always comparable with the next though it is of course, comparable with the same age group in a different five year period. It would obviously extend the histogram out of all reasonable proportion to have insisted upon equal age groups or, had they been made larger, would have obscured the period in which we are most interested, namely, the first two years of life. In the group attributed to primary disease of the central nervous system there are naturally more children/

children over three years of age than in the other group and there is only a little difference between the three periods in this. There is however, a marked difference in the age incidence of the first two years of life between the first and the other two five year periods. It will be seen that there is a preponderance of cases between six and eighteen months while in the other two periods there is the age distribution we would expect namely, preponderance in the first three months of life including all the cases of birth trauma or asphyxia and in older childhood with its epilepsy and inflammatory disease of the central nervous system. One is struck immediately by the fact that disease of the nervous system does not preclude the diagnosis of tetany and that when so many other acute infections are accompanied by tetanic manifestations it would be strange if acute inflammations of the meninges were exempt. Nevertheless if this were the whole answer one would expect a gradual transition from that of the first period through the second period and to the third instead of the abrupt change after 1922-26 that we see. However it will be remembered that there was a marked decrease in the number of cases of acute inflammatory disease of the central nervous system after the period 1922-26 and that this was in large part due to the fall in the number of cases of meningococcal meningitis admitted. After this period they were more often diagnosed as out-patients and sent direct to an Infectious Diseases/

Diseases Hospital. Meningococcal meningitis might therefore well account for the preponderance of infants in this age group.

In the age incidence of the convulsions that are not attributed to primary disease of the central nervous system we see a notable change through the years. In 1922-26 the peak is in the second half of the first year with the next six months a close second. In the second period the peak has transferred to the first three months with the second six months of life a close second. In the third period there is a peak only in the first three months of life and all other age groups are small in comparison. There has obviously been a fall in the relative proportions of children between the ages of six months and eighteen months who have had convulsions, in the last twenty-five years. Numerically there were always more children in the first six months of life who had convulsions than in the second but the age group six to eighteen months was of significant size in the past but is no longer so. This of course corresponds well with the hypothesis that there has been a fall in the spasmophilic group and is indeed what we might expect. But here again we must ask what has taken the place of tetany because the total numbers are not less.

In conclusion one may point out that in our cases of tetany there is an age incidence that corresponds very well with that of our first period and aids the contention that tetany/

tetany was an important factor in deciding the age incidence of the first two periods; more in the first than in the second.

DISTRIBUTION OF TYPES OF CONVULSIONS

If there does in fact exist a type of convulsion which has gone under the many names of "Gelegenheitskrampf", Initial Fever Convulsion, Incidental Convulsion and so on, and if this is distinct both from the convulsion of tetany on the one hand and from that of epilepsy on the other, it would be of enormous advantage if there were some clinical indications of the difference. In the literature there has been frequent reference to the initial character of the benign convulsion though this has been denied by Husler (1920) and also by Herlitz (1941) though the latter finds that though they do not frequently occur within the first few hours of illness they nevertheless are frequently within the first twenty-four hours. It would be interesting therefore to compare the type of convulsion met with in the various conditions and in the different periods. In allowing twenty-four hours for the initial convulsion we catch almost all those that would be so regarded by the average clinician and it is noteworthy that the classification adopted (page 69) was very easy to apply. There were very few cases where one wondered whether to class a convulsion or convulsions as initial or continued. Plate XV summarises/

summarises the findings expressed as percentages of the total number of convulsions.

Terminal convulsions scarcely need to be considered. I am least confident of the accuracy of the figures as it may often occur that a house physician does not bother to record a convulsion when a child is obviously dying or dead. They can ipso facto be diagnosed only in retrospect and any investigation of their character becomes almost impossible and probably unprofitable.

The other two types of convulsion are the most important and it can be seen at a glance that the initial convulsion is much more frequent in diseases not of the central nervous system than in those of the central nervous system. It is interesting to note that the convulsions of tetany resemble central nervous system disease in this respect and that a purely initial convulsion is less common in tetany. This is of particular interest when we note that in convulsions not attributable to primary disease of the central nervous system there has been a gradual diminution in the number of continued convulsions with an increase in the number of initial convulsions. This is seen only to a slight degree in the case of convulsions associated with primary disease of the central nervous system. There are two possible explanations for this. The one that here again is evidence that tetany is no longer the important factor in infantile convulsions that it was, and the other that it/

it is evidence of more prompt and effective therapeutics. As to the latter it seems to me to be unlikely though it is admittedly possible. The drugs used twenty-five years ago to control convulsions are the same as those used to-day. The more modern methods of phenobarbitone and phenytoin and so on are primarily prophylactics but chloroform, chloral hydrate and paraldehyde are the stand-bys to-day just as they were a quarter of a century ago.

THE DEGREE OF FEVER ON ADMISSION

It is perhaps doubtful whether one can draw any profitable conclusions from the degree of fever on admission but it is nevertheless interesting that we find yet again a gradual change in the pattern of incidence through the years. The number of convulsions that were afebrile in spite of evidence of an acute infection was much higher in 1942-46 than in 1922-26 and this was at the expense not of those with moderate fever but of those with high fever. In this connection it is a little hard to believe in the aetiological importance of pyrexia in spite of the ingenious demonstration of Herlitz (1941) when 30% are afebrile for the first twenty-four hours of admission and when only 16% reach a temperature of over 104°F. One may speculate upon the reason for this difference. It would seem unlikely to be due to treatment because most of these children come in at the beginning of the illness before it can have had any effect. One may claim tentatively/

tentatively that there has been a change in the aetiological factors in infantile convulsions in the last twenty-five years with a tendency for convulsions to appear at lower temperatures.

THE INCIDENCE OF CLINICAL RICKETS AND TETANY

The fall in both these two conditions scarcely needs any proof; it is common clinical knowledge and those who teach students have the same difficulty to-day in finding a case of rickets to demonstrate as they had in the past in finding a hospital-class patient without rickets. Plates XVII and XVIII show the actual fall in clinical rickets and tetany in these cases of convulsions and the fall has been striking in all cases whether of primary central nervous disease or not and whether associated with acute infection or not. It is interesting to note that this fall has been a progressive one in the thirties also and not only of recent origin. There was a marked fall before the Ministry of Food was conceived. Moreover this gradual fall with the middle period intermediate in degree is what we have seen in all the changing patterns of incidence whether of seasonal incidence or of age incidence or of degree of fever.

CONCLUSIONS

The pattern of incidence of convulsions has changed markedly since 1922. Whereas the convulsion typical of the twenties/

twenties was one occurring in an infant of around ten months and in the spring of the year; that of the later years was typically in a younger infant with no seasonal predeliction. The convulsion of the earlier period was more often repeated beyond the first twenty-four hours of the associated illness, it was more often febrile and it was more often associated with rickets or frank tetany. The convulsion of the 1940s is on the contrary usually truly initial, more often afebrile and the children are rarely rachitic and very rarely show signs of tetany.

The convulsion that ushers in an acute infection is, notwithstanding the other changes, no less common than it was before and indeed there is the distinct possibility that it is more common now than in the twenties.

Hypocalcaemia was the preponderant factor in the pathogenesis of incidental convulsions in infancy and childhood but is so no longer. There has been a steep but gradual fall in hypocalcaemia during the period under discussion and the gradient has increased in the last 15 years.

This fall in hypocalcaemia appears to have been masked by a compensatory increase in another factor the nature of which one can only speculate upon and this is better left until we come to consider the nature of the convulsive state.

IV - THE PRESENT SERIES

PREAMBLE

As a corollary to the retrospective study of the last chapter a contemporary clinical study is obviously desirable. Where the statistical study from its very remoteness obscures, the detail of the present series may illumine. Where the scanty numbers of the present series tempt false conclusions the statistics will correct.

Accordingly it was decided to make a critical study of every case of convulsions that was admitted to Professor Stanley Graham's wards at the Royal Hospital for Sick Children, Yorkhill, for a period of twelve months. In order to straddle the period in which we were most interested from the point of view of seasonal incidence it was decided to begin and end in the summer. The period selected was from the 1st of August 1947 until the 31st of July 1948 inclusive. The study was clinical and biochemical with the help of ancillary aids to diagnosis as and when required. The biochemical investigations were directed to the detection of hypocalcaemia and rickets. For this purpose the serum calcium, the plasma inorganic phosphate and the plasma alkaline phosphatase were determined in as many cases as possible. It was recognised that it would be difficult if not impossible to obtain blood from those who had only terminal convulsions and in only two such cases out of a total of 13 were/

were determinations made; this however is probably not of much importance. For the rest, determinations were made on all the other convulsions not due to primary disease of the central nervous system while in cases of central nervous system disease which acted as controls only five cases were missed for one reason or another.

METHOD

General

In each case the history was inquired into carefully to determine whether or not the child had a convulsion, its duration and whether there was a history of previous convulsions or not. The question of heredity has been considered by various authors without very much profit. In any case it was felt that the testimony of the parents in this connection was so often unreliable that little purpose would be served by trying to evaluate the familial factors.

The clinical examination was directed particularly towards the detection of organic disease of the central nervous system, and in almost every case a lumbar puncture was performed, and also the detection of clinical rickets including craniotabes and clinical tetany. No electrical reactions were done. Children of the age when rickets is likely and in whom there was any suspicion of enlarged epiphyses had their wrists X-rayed. Apart from this the usual ward investigation and treatment was instituted in each case.

Biochemical

The serum calcium was estimated by the method of Kramer and Tisdall (1921) (Harrison, 1947), the plasma inorganic phosphate by a modification of the method of Briggs (1922) and the plasma alkaline phosphate by a modification of the King-Armstrong method (Harrison, 1947; King, 1947). A detailed consideration of these methods is given in Appendix II.

GENERAL CONSIDERATIONS

During the twelve-month period 1st August 1947 to 31st July 1948 inclusive, there were 1,067 admissions to this medical unit. Of these, 64 cases (6%) had a history of convulsions or developed one or more convulsions during the stay in hospital.

As a preliminary it will be helpful to consider these cases under the same headings as those in the three five year periods already examined. A table summarising the findings of these cases is given in Appendix I. The cases are arranged in order of admission. Complete case-summaries have not been included as they would not contribute materially to the discussion as all the salient features have already been extracted but would merely swell unnecessarily the completed text.

DISEASES ASSOCIATED WITH CONVULSIONS

Table XXI shows the 64 cases of convulsions classified according/

according to diagnosis after the same plan as that for the cases in the preceding chapter (Table IV). It will be seen that cases attributed to primary disease of the central nervous system account for exactly half the total number of cases of convulsions. The same criteria of diagnosis have been adhered to. Epilepsy is only diagnosed where the clinical picture is unequivocal. No case appears twice and in each case of multiple diagnoses the primary disease with particular regard to the pathogenesis of convulsions was adopted.

There were 8 cases of idiopathic epilepsy. This gives a percentage of 12.5 which does not differ much from the corresponding figure of 15.4% for 1942-46, 15.2% for 1932-36 and 11.0% for 1922-26. Inflammatory disease of the central nervous system accounts for a higher percentage (18.7%) than that of any period since 1922-26 when it was 26.6%. The steady fall of the next two periods of 13.1% and 11.8% has not been maintained.

This hospital does not as a rule admit the new-born and the figures for "Birth Trauma" have been low in all periods.

The figure of 17.2% for mental deficiency is a marked increase on the three former periods. The steady rise can be seen thus:

1922-26	1932-36	1942-46	1947-48
5.9%	6.8%	13.6%	17.2%

The other half of the cases could not be attributed to primary disease of the central nervous system. Following the practice/

TABLE XXI

DISEASES ASSOCIATED WITH CONVULSIONS 1947-48

	Actual Figures	Percentage of Total
(1) Primary Disease of the Central Nervous System		
Epilepsy	8	12.5
Inflammatory Disease	12	18.7
Cerebral Haemorrhage	1	1.6
Mental Deficiency	11	17.2
Miscellaneous	-	-
Total	32	50.0
(2) Without Evidence of Primary Disease of the Central Nervous System		
Respiratory System		
Acute Respiratory Disease	17	26.6
Infectious Fevers	1	1.6
Miscellaneous	-	-
Total	18	28.2
Alimentary System		
Acute Infections	7	10.9
Miscellaneous	1	1.5
Total	8	12.4
Urinary Tract		
Total	3	4.7
Miscellaneous		
Convulsions of unknown aetiology	3	4.7
Tetany (Without infection)	-	-
Unclassified	-	-
Total	3	4.7
TOTAL	32	50.0
Total of All Cases	64	100.0
Total Admissions	1,067	
Convulsions as %age total admissions	6.0%	

practice of the classification in Table IV there was included a group of convulsions of unknown aetiology in those not attributable to primary disease of the central nervous system. As we shall see later these should be classed together with epilepsy but they number only 3 (4.7%) and will affect the proportions only slightly. The precise diagnosis of these cases will be considered later.

Disease of the respiratory system accounts for much the same proportion as in the past, 28.2% as opposed to 27.2% in 1942-46 and 29.7% in 1922-26 and of these most are acute respiratory disease. The figure for acute infections of the alimentary tract is also of much the same order as in the past. Of these there were 2 cases of ileo-colitis, both of which died in agonal convulsions. The "convulsions rate" for gastro-enteritis and acute ileo-colitis respectively is therefore 2.9% and 40%, the admissions of gastro-enteritis for the twelve months being 173 and for acute ileo-colitis being 5.

Convulsions associated with disease of the urinary tract comprised only 3 cases (4.7%). Of these one was the terminal convulsion of a chronic pyelonephritis, the other the terminal convulsion of nephrosis with gastro-enteritis and the other the initial convulsion of a hypertensive crisis in acute haemorrhagic nephritis.

There were no cases of tetany unassociated with an acute infection and no cases were unclassified. The three convulsions of unknown aetiology are/

are in a sense an admission of failure and the cases are detailed below.

Case No. 42. J.G. a boy aged eight weeks had melaena neonatorum at birth for which he was transfused with good result. He had an uneventful course thereafter until 4 days before admission when he had a short attack of twitching and loss of consciousness. This was repeated every day until admission when he had no further turns. On admission there was no abnormality to be made out. His serum calcium was 10.0 mgm.%. He was dismissed on 1.2.48. apparently well. On 14.3.48. he was re-admitted with acute gastro-enteritis and died six days later. Permission for post mortem examination was refused. He had no further fits after his first dismissal. The repeated minor attacks make it likely that this child would have continued to have fits in later life and should be regarded as a potential epileptic.

Case No. 52. G.B. a boy aged one week was admitted on 2.4.48. He was healthy at birth and nothing wrong was noticed until he was four days old when he began to have repeated short attacks of twitching. These continued. On admission he was slightly jaundiced but otherwise appeared healthy. He had a little fever and the only notable positive finding was a markedly positive Chvostek's sign. The serum calcium however was 9.4 mgm.%. The plasma inorganic phosphorus was unusually high, 8.0 mgm.%. A lumbar puncture revealed some red cells in the cerebro-spinal fluid but this was most likely due to the trauma of the needle. The child had no more fits and was dismissed home well on 23.4.48. This at first sight appeared to be a case of tetany of the newborn but in fact it bears out the finding that a facial phenomenon does not necessarily indicate hypocalcaemia. This case then belongs to the group of idiopathic convulsions of the newborn which we shall consider later.

Case No. 63. E.T. a girl aged one year and one month was admitted on 13.6.48. She had an uneventful history until she had measles ushered in with a convulsion at the age of eight months. She made good recovery and was well until she had a convulsion a propos nothing on 10.5.48. On 13.5.48. she had three more and during the last was brought up to Hospital. She incidentally received a severe burn of the right foot from a hot-water bottle during the ambulance journey. On examination the fontanelle was still patent but there were no/

no signs of rickets. No abnormality was detected. An X-ray of wrist showed no signs of rickets. Her serum calcium was 9.9 mgm. %, the plasma inorganic phosphorus 3.6 and the alkaline phosphatase was 11 K.-A. units. She had no more fits and but for the burn appeared quite well and bright. She was seen again as an out-patient on 3.9.48. when she gave a history of occasional minor fits after leaving Hospital but none latterly. This child is almost certainly an epileptic.

It seems likely that all these cases could be included under the group of epilepsy or at least of primary disease of the central nervous system. But as I hope to show, this distinction is not perhaps so important as it might seem.

On the other hand it enables us to calculate the percentage of cases associated with acute respiratory disease on the same basis as Herlitz (1941) and if we exclude these three cases we have 17 cases of acute respiratory disease in a total of 47 giving a percentage of 36.2% while that of acute infections of the alimentary tract is also increased, 14.9%.

MORTALITY

The mortality of the cases of convulsions admitted during this period is given in Table XXII. The position is complicated by the fact that 3 of the cases were transferred to a fever hospital. The two mentally defectives cannot be assumed to be alive as such children often succumb to an intercurrent infection; but if they are ignored for the moment, the mortality of cases attributed to primary disease of the central nervous system is 25.0% when the terminal convulsions are excluded, while the mortality from the others again excluding terminal/

terminal convulsions is 4.4%. It is interesting to note that the one death in this latter group was that of the one case of frank tetany met with in this survey.

TABLE XXII

Mortality in cases of convulsions admitted during the twelve-month period August 1947 to July 1948.

	Primary Disease of the C.N.S.	Others	Total
Total Number of Deaths	11	10	21
Terminal Convulsions	4	9	13
Deaths Excluding Terminal Convulsions	7	1	8
Cases Transferred	2*	1**	3
Mortality Excluding Terminal Convulsions	25%	4.4%	18.6%

* Both mental defectives with measles. ** Measles.

SEASONAL INCIDENCE

The figures for only one year are too small to do more than complement our previous findings. It is more indeed for the sake of completeness that the seasonal incidence of the total cases and of the cases divided into those attributed to primary disease of the central nervous system and others, are given in Table XXIII. The outstanding February peak of the primary nervous cases was due to five epileptics/

epileptics and some cases of meningitis. The seasonal incidence of the other cases offers nothing new.

TABLE XXIII

Seasonal Distribution of Cases of Convulsions Admitted During the Twelve-Month Period August 1947 to July 1948

Month	Total Admissions	Total Cases	Primary Disease of the C.N.S.	Others
1947				
Aug	75	4	1	3
Sep	79	2	2	-
Oct	95	7	3	4
Nov	87	5	2	3
Dec	94	7	3	4
1948				
Jan	85	3	-	3
Feb	85	15	10	5
Mar	94	6	5	1
Apr	93	5	2	3
May	97	7	3	4
June*	106	3	1	2
July*	77	-	-	-
TOTAL	1067	64	32	32

(* With the introduction of the National Health Service on the 5th of July all records were closed and re-opened on that day. The figures for June therefore include the first four days of July while those for July begin with the fifth day.)

AGE INCIDENCE

The age incidence is shown in Table XXIV. It will be seen that in the cases attributed to primary disease of the central/

central nervous system 12 out of the 32 were under one year of age and exactly one half were under (16 cases) two years of age. 6 were in the tetany age-group of six to eighteen months. Of the first two years there were 7 in the first six months, 5 in the second and 1 in the third. The peak incidence is in the first three months of life. 13 cases were over three years of age.

In the cases not attributed to primary disease of the central nervous system there were 18 cases under one year and 24 cases under two years of age. There were 10 cases in the age-group six to eighteen months. There were 11 cases in the first six months of life, 7 cases in the second and 3 cases in the third. There is a marked peak incidence in the first three months of life. Only 5 cases were over three years of age.

TABLE XXIV

Age Incidence of Cases of Convulsions Admitted During the Twelve Month Period August 1947 to July 1948

Age-Group Years	Primary Disease of the C.N.S.	Others
0 - 3/12	5	9
3/12 - 6/12	2	2
6/12 - 12/12	5	7
12/12 - 18/12	1	3
18/12 - 2	3	3
2 - 3	3	3
3 - 5	5	2
Over 5	8	3
TOTAL	32	32

Only five neonatal cases are included in this series (Case Nos. 7, 8, 34, 52 and 64). Cases 7 and 8 were both of pyloric stenosis who though successfully operated upon were re-admitted with gastro-enteritis and died in terminal convulsions. The remainder are worthy perhaps of more detailed consideration.

Case No. 34. J.R. a boy aged five days was admitted on 18.2.48. He was born spontaneously after a normal pregnancy but after birth moaned incessantly, would not suck, was seen to be jaundiced on the second day and developed an increasing oedema. He was a very small child but grossly oedematous, afebrile and jaundiced; the spleen was palpable two fingerbreadths below the costal margin. There was spontaneous nystagmus and the child had two generalised convulsions. The haemoglobin was 15.65 gms.% and the reticulocyte count was 3%. The child died before further investigation could be carried out; he was indeed too ill. A post mortem examination revealed a pneumococcal meningitis. The child almost certainly had a septicaemia but whether rhesus factor incompatibility entered into the picture could not be determined. The mother was still in bed and lived outside Glasgow and blood could not be obtained.

Case No. 52 is described on page 125.

Case No. 64. D.R. was a boy aged ten days and was admitted on 23.6.48. He was born spontaneously at home after a normal pregnancy and seemed healthy at birth. On the day before admission when he was nine days old he began convulsing; he had been previously quite well. The convulsions were generalised and continued at frequent intervals until admission. He refused feeds but did not vomit; he had frequent loose stools after administration of milk of magnesia by his mother. On admission he looked ill but was afebrile. Chvostek's sign was positive but no other signs of disease could be detected. The convulsions were controlled by chloral hydrate but the child collapsed and died the next day. The serum calcium was 14.5 mgm.%, the plasma inorganic phosphorus was 5.5 mgm.% and the W.R. was negative. Post/

Post mortem examination showed signs suggesting a generalised septicaemia together with a haemorrhagic pneumonia. There was in addition a marked degree of porencephaly.

It is interesting that two of these children had a facial phenomenon in spite of a normal or high serum calcium. In two of them there was an acute infection and in one there was a developmental abnormality of the brain as well. Only one of them (Case 52) could perhaps be classed as "idiopathic convulsions of the newborn" (Thomson, 1921). These are described as frequent fits occurring in the first few weeks of life with a good prognosis and have also been attributed to hypocalcaemia (Graham, 1933). In this case there was nothing in the history to suggest asphyxia or "birth trauma" while there was also no hypocalcaemia.

DISTRIBUTION OF TYPES OF CONVULSION

Table XXV shows the distribution of types of convulsion. It has been more easy to assess precisely the type of convulsion in these cases that were studied personally than in those extracted from the case records. It will be seen that if we exclude the terminal convulsions, the great preponderance of cases associated with disease of the central nervous system (21 out of 28) are continued while 20 out of 23 cases which are not associated with primary disease of the nervous system were on the other hand initial. The three cases of continued convulsions/

convulsions in the latter group include two cases (Nos. 52 and 63) of "convulsions of unknown aetiology" which, as has already been suggested, might more properly be relegated to the other group. This would leave only one case of convulsions not associated with primary disease of the central nervous system that had convulsions continued beyond the first twenty-four hours of the illness. This child (Case No. 61) was one of broncho-pneumonia admitted with the history of a short convulsion. He had high fever and was dehydrated. He remained acutely ill and had another short generalised convulion three days after admission. He thereafter made an uninterrupted recovery. He was seen again as an out-patient about a month later when he had had no more fits but still had a loose cough and a skiagram showed partial collapse of the lower lobe of the left lung.

TABLE XXV

Type of Convulsion Met With in the Twelve-Month Period August 1947 to July 1948.

Type of Convulsion	Total	Convulsions associated with Primary Disease of the C.N.S.	Convulsions not associated with Primary Disease of the C.N.S.
Initial	27	7	20
Continued	24	21	3
Terminal	13	4	9
Total	64	32	32

It will be seen that a continued convulsion is strongly in favour of a primary central nervous origin of the fit. On the other hand an initial convulsion is occasionally the harbinger of acute inflammation of the central nervous system, and cannot ipso facto be regarded as benign.

DEGREE OF FEVER ON ADMISSION

Table XXVI shows the degree of fever recorded on admission; these are as before all rectal temperatures, and the highest temperature recorded during the first twenty-four hours of admission is taken.

TABLE XXVI

Degree of Fever	Primary Disease of C.N.S.		Others	
Afebrile	14	43.7%	9	28.9%
Over 100.4°F but under 102°F	5		6	
Over 102°F but under 104°F	6	11 34.4%	6	12 37.5%
Over 104°F	7	21.9%	11	34.4%
Total	32		32	

As might be expected there are more cases of primary disease of the central nervous system that are afebrile. The other figures accord more or less with those for 1942-46 except/

except that there are more cases with a temperature of over 104°F. It must be admitted however that the figures are small.

PREVIOUS CONVULSIONS

A history of previous convulsions was obtained in only 16 out of the 64 cases; that is 25%. This does not give a true picture of the probabilities entailed. A history of previous convulsions is not only a function of the degree to which there is a tendency to recurrent convulsions but also of the patient's age. Ceteris paribus, the younger the patient is, the less likely he is to give a history of previous convulsions. Similarly, the younger the average age of a series, the smaller will be the proportion with previous convulsions. One may recall here that the age incidence of the present series shows a much younger peak than that of the twenties and one would expect from this alone, a smaller proportion of cases with a history of previous fits. Of these 16 cases, 9 were epileptic and 6 were mentally defective. Only one case was assigned to the group not attributed to primary disease of the central nervous system and that only doubtfully so, being one of the "convulsions of unknown aetiology" already discussed (Case No. 63).

THE INCIDENCE OF RICKETS AND TETANY

Clinical manifestations of rickets were found in only 3 cases. One/

One of these (Case No. 37) had marked bossing and craniotabes and had also a positive Chvostek's sign. This case had a serum calcium of only 5.1 mgm.% and a plasma inorganic phosphorus of 10.0 mgm.%; this is the only case of frank tetany in the series. The second was an overgrown mentally defective child (Case No. 49) with recurrent fits. The third (Case No. 16) is of some interest in that the child was fed large quantities of various preparations of vitamin D, bathed in ultra-violet light and taken to innumerable clinics because of a delay in closure of the anterior fontanelle in the absence of any other signs whatever of rickets. The fontanelle was 2 x 1 fingerbreadths at the age of nineteen months. X-ray of wrist showed normal ossification and the serum calcium was 11.0 mgm.% and the plasma inorganic phosphorus was 4.0 mgm.%; the plasma alkaline phosphatase was 12 K.-A. units. The child had a minor fit at the onset of an upper respiratory infection.

Radiological evidence of rickets was seldom sought. In one case with unequivocal evidence, both clinical and biochemical, of rickets, the X-ray nevertheless showed no signs of rickets. This is not surprising in the light of the British Paediatric Association Report (1944) and also a survey by Graham (1942) in which the superiority of biochemical and even clinical criteria over routine radiology was clearly demonstrated.

Clinical evidence of tetany was seen in three cases, two/

two of which have been discussed already; the finding of a positive Chvostek's sign in the newborn was not accompanied by the finding of a lowered serum calcium. One case of frank tetany was found and the case history is given below.

Case No. 37. B.L. was admitted at the age of seventeen weeks on 20.2.48. He was the fifth child of the family and was healthy at birth. He was breast fed for 8 days and then fed on cow's milk with Sister Laura's food. He was given no cod-liver oil, or substitute. He throve well until the day of admission (20.2.48.) when he had a convulsion lasting 20 minutes; this recurred at frequent intervals during the day. He was admitted in an acutely ill condition with high fever, grunting respirations and a cyanotic tinge of the lips. There was marked frontal bossing and craniotabes but not very obvious enlargement of the epiphyses. There were marked signs of broncho-pneumonia at both bases. The child convulsed at intervals and in spite of penicillin, sulphonamide, oxygen and calcium, he died the next day. The serum calcium was 5.1 mgm.%, the plasma inorganic phosphorus 10.0 mgm.% and the plasma alkaline phosphatase was 47 K.-A. units. The child was too ill to be X-rayed.

BIOCHEMICAL SURVEY

The normal adult serum calcium level is 9.0 - 11.5 mgm.% (Peters and Van Slyke, 1931). In infancy it lies rather higher; 10.0 - 11.5 mgm.% (Howland and Kramer, 1921). Spasmophilia develops when the serum calcium falls below 7.0 mgm.% unless there is a concomitant rise in the hydrogen concentration of the blood or a fall in the serum protein (Peters and Van Slyke, 1931, Kramer, Tisdall and Howland, 1921, Howland and Marriott, 1918). The serum calcium is diminished in only two conditions, tetany and nephritis (Howland and Kramer, 1921).

Inorganic/

Inorganic phosphates are present in the body in two forms, solid calcium phosphate in the bones and the dissolved phosphates of the blood (Peters and Van Slyke, 1931). The inorganic phosphate of the plasma of children expressed as mgm.% of phosphorus ranges from 4.5 to 6.8 with an average of 5.4 as opposed to that of adults which averages 2.1 mgm.%. In rickets the inorganic phosphorus is 1.0 - 3.2 mgm.% (Howland and Kramer, 1921).

The normal alkaline phosphatase by the King-Armstrong method is given as 3 - 13 units (Harrison 1947) and 5 - 10 units (King 1947). The average figure met with in rickets is given as 30 K.-A. units (Panton, Marrack and May, 1945).

CASES OF PRIMARY DISEASE OF THE NERVOUS SYSTEM

The serum calcium, plasma inorganic phosphate expressed as phosphorus and the alkaline phosphatase were determined in 23 cases. Four cases were terminal and the other five were omitted for various reasons. As these were to be regarded as more or less controls 23 cases are more than adequate. Table XXVII lists the results.

Serum Calcium

It will be seen from the Table and also from Plate XX that these all fall within normal limits except one. Moreover the distribution is seen to approximate to the "normal" in type. The one rather high figure in Case No. 64 was obtained from/

TABLE XXVII

SERUM CALCIUM, PLASMA INORGANIC PHOSPHORUS AND PLASMA ALKALINE PHOSPHATASE IN CASES OF CONVULSIONS ADMITTED IN THE TWELVE-MONTH PERIOD AUGUST 1947 TO JULY 1948

Convulsions attributed to primary disease of the C.N.S.			
Case Number	Calcium mgm.%	Phosphorus mgm.%	Phosphatase K.-A units
3	10.0	4.6	20
5	11.4	4.5	16
9	10.2	3.7	19
10	9.8	5.1	5
12	12.3	4.7	13
14	8.3	3.9	-
21	9.9	4.2	13
24	10.0	3.0	6
29	10.0	4.2	5
30	10.2	4.2	7
32	9.9	3.7	14
35	11.5	3.3	5
36	9.1	4.6	12
38	10.6	3.8	-
39	10.7	5.4	18
41	9.8	4.5	10
43	10.0	3.3	-
47	10.2	4.4	5
48	9.4	3.5	3
49	9.7	1.9	19
50	9.3	3.7	8
55	10.7	3.4	10
64	14.5	5.5	5

No estimations were performed on Cases No. 6, 18, 20, 34, 44, 51, 53, 57 and 59. Four of these cases had terminal convulsions only.

from a dehydrated child in extremis.

Plasma Inorganic Phosphorus

All but one of these lie between 3 and 6 mgm.% with a peak between 3 and 4 mgm.%. This is perhaps a little lower than that usually accepted as normal (Mitchell-Nelson 1946, Harrison 1947). The one low phosphorus of 1.9 mgm.% (Case No. 49) was associated with obvious clinical rickets. These results are shown graphically in Plate XXI.

Plasma Alkaline Phosphatase

Plate XXII shows a peak between 5 and 10 units which accords well with the accepted normal (Harrison 1947, King 1947). A certain number of cases however fall above that range and 6 cases lie above 15. It is likely however that in view of the very high figures obtained in frank bone disease (ibid) that the normal variation is somewhat wider than 5 to 15 units. It is noteworthy that the one case of clinical rickets who had a low plasma phosphorus had not strikingly high phosphatase, (19 units).

CASES NOT ATTRIBUTED TO DISEASE OF NERVOUS SYSTEM

The same estimations were made on 25 cases of convulsions not attributed to primary disease of the nervous system, (Table XXVIII). The seven cases in whom no determination was made all had terminal convulsions in whom the children were dead before blood could be obtained. It was in any case not/

TABLE XXVIII

SERUM CALCIUM, PLASMA INORGANIC PHOSPHORUS AND PLASMA ALKALINE PHOSPHATASE IN CASES OF CONVULSIONS ADMITTED IN THE TWELVE-MONTH PERIOD AUGUST 1947-JULY 1948.

	Convulsions not attributed to primary disease of the C.N.S.		
Case Number	Calcium mgm.%	Phosphorus mgm.%	Phosphatase K.-A units
1	10.3	4.5	11
11	10.1	4.3	9
13	7.0	3.5	10
15	10.1	11.1*	-
16	11.0	4.0	12
17	9.5	3.0	5
19	9.9	4.0	-
22	9.6	2.5	2
23	8.5	9.7*	-
25	9.8	4.5	11
26	10.4	3.5	9
27	9.9	3.4	22
28	10.2	4.0	5
31	9.6	4.0	8
37	5.1	10.0*	47
42	10.0	6.4	4
45	11.3	3.2	3
46	9.4	3.4	4
52	9.4	8.0	-
54	10.0	3.4	4
58	10.3	4.2	8
60	9.8	3.4	10
61	10.1	3.1	8
62	10.1	3.2	6
63	9.9	3.6	11

* in extremis

No estimations were carried out in the following cases, Nos. 2, 4, 7, 8, 33, 40 and 56, all of which had terminal convulsions.

not thought to be necessary to strive particularly to obtain samples from such cases though two were in fact done, Nos. 15 and 23.

Serum Calcium

Plate XX shows the distribution of the serum calcium in these cases. It will be seen that here too the majority of cases fall between 8 and 10 mgm.%. There are however two cases with values below 7 mgm. and which must be regarded as abnormal. One of these we have already discussed and there can be no doubt that it was a true case of tetany. The other, Case No. 13, presents rather a problem.

Case No. 13. M.W. a girl aged twelve months was admitted on 22.10.47. She was healthy at birth and was bottle fed from birth with Full-Cream National Dried Milk. In addition she was given two teaspoonfuls of cod-liver oil daily. Mixed feeding was started at nine months. She was quite well until the day of admission when she had a short convulsion. On admission she had a temperature of 101.2°F. and was found to have enlarged and inflamed tonsils. She also had some purulent nasal discharge. Otherwise there was nothing abnormal detected. X-ray of wrist showed normal ossification. The serum calcium however was 7.0 mgm.% and the plasma phosphorus 3.5 and the plasma alkaline phosphatase was 9.5 units. The serum calcium was repeated two days later and was 8.2 mgm.%. She was dismissed home well on 26.10.47. and was seen again as an out-patient on 4.11.47. when she appeared quite well and had no more fits.

That this child had a degree of hypocalcaemia there can be no reasonable doubt though it is difficult to correlate the finding with either the history or the clinical examination.

Plasma Inorganic Phosphorus

Plate XXI shows graphically the plasma phosphorus of these cases. It will be seen that there is here also a fairly normal distribution that accords well with that of the other group shown on the same chart. There are however a number with a high plasma phosphorus. Three of these cases were in extremis and a terminal renal failure is probably sufficient to account for this. In the other, Case No. 52 already discussed, the phosphate retention is probably physiological and related to the poor renal function of infancy (Young and McCance 1942). Otherwise we see again the tendency for the phosphorus levels to be rather on the low side.

Case No. 22, a child of seven years three months of age with pneumonia had a low plasma inorganic phosphorus of 2.5 mgm.%. There is no reason to believe that this child had rickets and it is interesting to recall that Gerstenberger and his associates (1923) found similar low values in lobar pneumonia in the absence of signs of rickets.

Plasma Alkaline Phosphatase

Plate XXII shows the distribution of the alkaline phosphatase levels among these cases. But for two cases there seems to be a rather more normal series of values in these cases. One case with the highest level had frank rickets and tetany, the other, Case No. 27 had no other indication of disordered/

disordered calcium metabolism and the finding can perhaps be ignored.

To recapitulate, if one examines the three Plates, XX, XXI, XXII there is on the whole a strikingly normal distribution of all the biochemical findings. One cannot escape the conclusion therefore that a manifest hypocalcaemia is a negligible aetiological factor in convulsions to-day and furthermore that there is no evidence of rickets (biochemically) except in a very small minority of cases.

DISCUSSION

The cases investigated confirm Peterman's (1932) assertion that convulsions in infancy and childhood are associated with certain diseases and that neither the "teething fit" nor that due to indigestion in fact occurs. In only 3 of the cases could the diagnosis not be made with certainty and in these, as we have seen, the probable diagnosis was epilepsy. Moreover in those cases where epilepsy or mental deficiency were diagnosed no doubtful cases were included, they were all obvious clinical diagnoses. That being so, one can jettison a great deal of the argument that has occupied the last century. We are left with convulsions due to direct stimulation of the brain by pathological processes, to indirect stimulation in systemic disease and to the/

the spontaneous convulsive state.

The marked rise in the number of admissions of mentally defective children with convulsions that was noted on page 122 has been maintained. Here again one must beware of concluding that this necessarily indicates an absolute increase in the incidence though the figures are suggestive. The increase in the number of epileptics admitted on the other hand has not been maintained and indeed if we compare the figures in Table IV with the present one of 12.5% it will be seen that there is no significant difference.

There is nothing more to add to what has been said on the subject of seasonal incidence but with regard to age incidence it is interesting to note that the picture of a preponderance in the first three months of life is maintained. Moreover it is worth noting that in those convulsions associated with systemic disease there were only 5 cases out of 32 that were over three years of age and only 8 over two years of age. The problem of the non-epileptic and "non-organic" convulsion is primarily one of the first two years of life and especially of the first three months.

With regard to types of convulsions it is established I think, that the "initial convulsion" is truly initial in that it occurs within the first twenty-four hours of an illness and that anything else should be regarded with the gravest suspicion. Similarly this initial type of convulsion is one that/

that happens usually only once in the child's lifetime and a history of a previous convulsion should be regarded as highly suspicious of epilepsy.

Of the incidence of rickets and tetany and of the importance of hypocalcaemia it is abundantly proved that whatever may have been the position in the past, there is a virtual disappearance of both from the clinical scene.

V - SPECULATIONS AND CONCLUSIONS

"Parturient montes, nascetur ridiculus mus"

(Horace, Ars Poetica)

THE NATURE OF INFANTILE CONVULSIONS

We have followed the changing views of physicians through the ages and studied the manifold contributions of the present century; we have also searched the records of a quarter-century and examined in detail our own cases. I think that there is a real lesson to be learnt from our essay into history. If we smile at the credulity of the ancient masters of medicine we must the more admire their discernment. But it is not of the general lesson of history that I would write now but of its direct contribution to the pathogenesis of infantile convulsions. There has been a constant struggle to relate every convulsive seizure to an obvious cause. It was manifestly impossible that there should be only one such cause when convulsions arose in such differing conditions, but the convulsion would not on that account have attracted such attention. It was in itself an alarming manifestation but even so it might have been relegated to the position of a terrifying symptom such as delirium. Unfortunately the symptom bore no relationship whatever to the degree of illness and moreover was also quite frequently seen arising spontaneously with no other/

other indication of disease before or after the fit. Accordingly more and more causes were adduced and yet none of them, not even organic disease of the brain, were invariable in their effect. This tendency to regard almost any preceding event as an aetiological factor was carried beyond the bounds of reason but it nevertheless displayed an attitude common even to-day in which the proximate and ultimate causes are confused.

If a large number of factors all differing in kind and degree can some times but not always produce a convulsion, only a limited causal relationship can be attributed to these various factors and they can at best only be proximate causes. This led to the twentieth century view of the hyperexcitability of the infantile nervous system which was, as we have seen, never very satisfactory. This view premised that the individual had a convulsion by virtue of his youth rather than that the infant had a convulsion by virtue of a tendency inherent in the individual. The former opinion is unsatisfactory in that only very few children have convulsions, while they are after all, all young; furthermore there is no correlation between the degree of provocation and the appearance of a fit. Against the latter theory that all infantile convulsions are the result of an innate proclivity is the objection that most of these children have no more convulsions. We may take as a conservative estimate that about 12% of infantile convulsions are/

are followed by recurrence and that means of course that 88% have no more fits. What then has happened to the convulsive tendency which was not confined to the 12%?

The discovery of tetany and more particularly of latent tetany appeared at first to be the solution. Here was a metabolic upset which was more or less confined to the age group of maximum incidence of convulsions which in itself predisposed to convulsions. Tetany would explain not only the convulsions of infancy but also their cessaion. Nevertheless the sceptic will note that not all children with tetany had convulsions even in the presence of an acute infection. Most children with hypocalcaemic convulsions had their convulsions coincident with the onset of an acute infection although as we have seen these convulsions in frank tetany at least were often continued beyond the first twenty-four hours of illness. There is a very interesting suggestion as to how latent tetany, a minor and probably therefore a more widespread degree of the same metabolic upset, might be responsible for the initial convulsion of an acute infection. We know that it is upon the ionised moiety of the circulating calcium that the neuromuscular excitability depends and that the degree of ionisation depends, other things being equal, upon the acid-base balance of the blood. An alkalaemia will depress ionisation and render the neuromusculature more excitable while an acidaemia will do the reverse. Obviously then an alkalaemia would convert latent tetany/

tetany in which the ionised calcium just meets requirements and no more, into frank tetany in which the ionised calcium is inadequate to restrain the neuromuscular excitability. There is abundant evidence that the onset of pyrexia whether produced artificially or in disease is accompanied by a temporary alkalaemia. (Hill and Flack, 1909, Bazett and Haldane, 1921, Koehler 1923, and White 1925). This of course is only temporary and increased catabolism produces an over-compensation thereafter. A temporary change is all that would be required to initiate a convulsion at the beginning of an infection in a child whose ionic calcium equilibrium was precarious. As it was perfectly reasonable to suppose that latent tetany would be more widespread than frank tetany and that conditions which produced the one would produce the other, it seemed a logical corollary that many more convulsions were due to latent tetany than to frank tetany. The signs of latent tetany were usually in abeyance during and immediately following a convulsion and the serum calcium was not always significantly low; the diagnosis could therefore only be made by analogy. It is here that the seasonal incidence described by Graham (1932, 1933) completed the picture and appeared to solve the problem of the aetiology of infantile convulsions.

In the foregoing survey we were able to conclude without any reasonable doubt that frank tetany had virtually disappeared from the clinical scene and that rickets also was

a/

a comparative rarity. Under these circumstances it is no longer possible to postulate a latent tetany causing the remaining convulsions. Moreover these convulsions have by no means diminished in number. We are therefore forced to one of two conclusions:- one, that the fall in hypocalcaemic convulsions has been compensated for by the fortuitous rise in the incidence of another and unknown aetiological factor; the other conclusion which is the one that I would tentatively submit is that hypocalcaemia was never an ultimate cause of convulsions but that the spasmophilic diathesis merely acted as a proximate cause thereby determining the seasonal and age distribution without affecting the total incidence. I would submit that no cause yet cited can be satisfactorily regarded as anything more than a precipitating factor. It is significant that it is the neurologist in the past who has insisted upon the unity of all convulsions; and if he has excepted the "teething spasm" or tetany from his concept perhaps this is rather from his own unacquaintance with these two conditions than a logical necessity. It is the paediatricians who have urged for generations the exclusiveness of the infantile fit.

It may perhaps be permitted to venture yet further upon the shifting sands of speculation and discuss the nature of the ultimate cause of convulsions. We have seen that a convulsion may be spontaneous or that it may be provoked by some obvious stimulus/

stimulus and that there is no correlation between the type or degree of stimulus and the convulsion. In certain people then a certain stimulus will provoke a convulsion; a convulsion in itself will cause a certain amount of brain damage and this will lower the convulsive threshold and lead to spontaneous recurrence but only in those whose threshold is already particularly low. In other words we may postulate a convulsive tendency which varies only in degree. In the highest degree it results in spontaneous convulsions or idiopathic epilepsy; at the other end of the scale only the provocation of a severe stimulus will produce the fit, such as in acute inflammation of the meninges, cerebral oedema and so on. Intermediate on the epileptic side are those convulsions called by Stauder (1939) Provoked Epilepsy, while intermediate on the other side are the initial convulsions of infancy. Peterman (1932) has already pointed out that the high incidence of convulsions in childhood is due to the high incidence of acute infections in this period and it is not unreasonable to suppose that in an individual with a slightly lowered convulsive threshold, the concatenation of circumstances required to provoke a convulsion, is most likely to occur in infancy and indeed will often happen only once in a life time.

I would therefore classify all convulsions as (a) spontaneous or (b) provoked.

Spontaneous convulsions are those in which the convulsions/

convulsions occur in the absence of any precipitating factor and are dependent entirely upon the inherent convulsive tendency. They would of course include cases of idiopathic epilepsy and the convulsions associated ab initio with mental defect and usually with demonstrable developmental abnormalities of the brain. They would also include those with permanent brain damage. Provoked convulsions are those in which the inherent convulsive tendency is insufficient to give rise to a convulsion in the absence of an adequate stimulus each time. Such convulsions are those associated with acute inflammation of the meninges, tetany, uraemia and the initial convulsions of acute infections. Furthermore, in certain borderline cases a provoked convulsion will cause sufficient damage to the brain to tip the scale in favour of spontaneous convulsions thereafter.

Obviously there is no reason why one should not follow the neurologists' practice and speak of spontaneous or provoked epilepsy, instead of convulsions. There is nothing in the above argument against this and moreover it would have the advantage of including explicitly petit mal, uncinate fits and epileptic equivalents. I am doubtful of the validity of including migraine and in any case the question is not relevant to the present discussion. Other forms of epileptic response however could easily be attributed to slight differences in kind of the convulsive threshold.

The/

The word epilepsy is firmly entrenched in clinical usage and has been since the days of Hippocrates; to extend its meaning so radically as has been suggested is to my mind quite unjustified and has, as we have seen, been the cause of much misunderstanding. We can instead retain the word convulsion in the classification but with the proviso that it must suggest a rather wider meaning and include other related seizures.

For this reason the term epilepsy is not used in so wide a connotation but I would emphasise that the word is retained as describing a well-known clinical picture and in no wise implies a fundamental basis that differs from that of other convulsions.

The most that can be claimed for this classification is that it is simple and at least as accurate as many others. When one compares it with that offered by a current textbook (McQuarrie, 1946) the value of its simplicity is enhanced.

It may well be that rash speculation has been allowed to burst the bonds of prudence and that I have wandered far from the safe foot-holds of observed facts. In extenuation I would point to the recent literature and in particular to the current textbooks and suggest that "truth comes more readily from error than from confusion."

CONCLUSIONS

We may now summarise the main conclusions that are submitted as a result of this investigation.

(1) There has been no fall in the incidence of convulsions in children in the last quarter of a century and there may have been an increase.

(2) The pattern of incidence of convulsions not attributed to primary disease of the central nervous system has changed profoundly since 1922. This is considered to be due to the virtual disappearance of hypocalcaemia as an aetiological factor.

(3) An explanation of the apparent contradiction implied in these two conclusions is put forward:

   (a) that all convulsions are primarily due to an inherent and often innate convulsive tendency and

   (b) that this convulsive tendency varies in degree from that responsible for spontaneous recurrent convulsions (or idiopathic epilepsy) to that which is responsible for a convulsion only on the extreme provocation of gross cerebral irritation.

(4) A simple classification of convulsions is therefore tentatively suggested, namely, that convulsions may be classed as either

   (a) spontaneous or

   (b) provoked

(5)/

(5) **The prognosis of infantile convulsions varies inversely with the degree of provocation responsible for the convulsion.**

APPENDIX I

The following table summarises the findings in the cases investigated. They are arranged in order of admission.

EXPLANATION OF TERMS.

Age	in years
Sex	M = male, F = female
Previous convulsions	+ = a history of previous convulsions
Type of fit	I = Initial, C = Continued and T - Terminal. For further definition see text, page 69
Grade of fever	see text, page 69
Acute infection	+ or - indicates presence or absence
Clinical rickets	+ or - indicates presence or absence
Clinical tetany	+ or - indicates presence or absence
X-ray	+ or - indicates presence or absence of radiological evidence of rickets
Serum calcium	in mgm.%
Plasma phosphorus	in mgm.%
Plasma phosphatase	alkaline phosphatase in King-Armstrong units

Abbreviations.

N.D. = not done. Transf. = transferred to another hospital.

Case Number.	Initials	Age	Sex	Date of Admission	Previous Convulsion.	Type of Fit I, C or T.	Grade of Fever. +, ++, +++.	Acute Infection.	Clinical Rickets.	Clinical Tetany.	X-ray	Serum Calcium.	Plasma Phosphorus	Plasma Phosphatase.	Diagnosis	Results	Comments
1	M.H.	3/12	F	10.8.47.	-	I	+	+	-	-	-	10.3	4.5	11	Gastro-enteritis	Well	
2	C.W.	1.3/12	F	16.8.47.	-	T	+++	+	-	-	N.D.	N.D.	N.D.	N.D.	Gastro-enteritis Broncho-pneumonia.	Died	P.M. Striking phlegmonous oesophageitis and gastritis. Marked enteritis and fatty liver.
3	A.A.	8.11/12	F	22.8.47.	+	C	-	-	-	-	-	10.0	4.6	20	Epilepsy	I.S.Q.	Uncontrolled by phenobarbitone: post-epileptic automatism.
4	R.G.	8/12	M	22.8.47.	-	T	-	-	-	-	N.D.	N.D.	N.D.	N.D.	Chronic Pyelonephritis	Died	Confirmed at P.M. Died shortly after admission - no investigations.
5	G.K.	1.10/12	F	1.9.47.	+	C	++	+	-	-	N.D.	11.4	4.5	16	Mental Deficiency Measles	Transf.	Some microcephaly.
6	J.McL.	5 yrs.	F	22.9.47.	+	C	-	-	-	-	N.D.	N.D.	N.D.	N.D.	Mental Deficiency Epilepsy	I.S.Q.	Later admission 1.4.48. when biochemistry done.
7	R.R.	3/52	M	3.10.47.	-	T	++	+	-	-	N.D.	N.D.	N.D.	N.D.	Pyloric stenosis. Broncho-pneumonia.	Died.	Also gastro-enteritis and fatty liver at P.M.
8	J.S.	3/52	M	4.10.47.	-	T	+	+	-	-	N.D.	N.D.	N.D.	N.D.	Pyloric stenosis Gastro-enteritis	Died.	P.M. Jaundiced, hepatic fatty change with bile thrombi.
9	D.C.	2/12	M	6.10.47.	-	C	+++	+	-	-	N.D.	10.2	3.7	18.8	? Intracranial haemorrhage. Gastro-enteritis.	Well	Xanthochromic C.S.F.
10	I.D.	2.11/12	F	10.10.47.	+	C	-	-	-	-	N.D.	9.8	5.1	5	Mental Deficiency	I.S.Q.	Encephalogram normal. Hemiparesis. Asphyxia at birth. "Salaam" type.
11	F.McD.	5/365	F	13.10.47.	-	I	+++	+	-	-	N.D.	10.1	4.3	9	Upper Respiratory Infection.	Well	Seen 10.11.47. - no fits.

Case Number	Initials	Age	Sex	Date of Admission	Previous Convulsion.	Type of Fit I, C or T.	Grade of Fever. +, ++, +++.	Acute Infection.	Clinical Rickets.	Clinical Tetany.	X-ray	Serum Calcium.	Plasma Phosphorus	Plasma Phosphatase.	Diagnosis	Results	Comments
12	J.M.	9/12	M	15.10.47.	+	C	++	+	-	-	-	12.3	4.7	13	Mental Deficiency Broncho-pneumonia.	Died	Confirmed at P.M. Blind.
13	M.W.	1 year	F	22.10.47.	-	I	++	+	-	-	-	7.0	3.5	9.5	Upper Respiratory Infection.	Well	Seen as O.P. 4.11.48. No fits.
14	E.M.	5 years	M	1.11.47.	+	C	++	+	-	-	N.D.	8.25	3.9	-	Idiocy. Broncho-pneumonia.	Died	Confirmed at P.M. W.R. negative.
15	J.C.	3/12	M	2.11.47.	-	T	++	+	-	-	N.D.	10.1	11.1	-	Ileocolitis.	Died	Confirmed at P.M.
16	M.F.	1.7/12	F	4.11.47.	-	I	+	+	(+)	-	-	11.0	4.0	12	Upper Respiratory Infection.	Well	Fontanelle 2 x 1 in spite of adequate Vit. D. Seen 29.12.47. Well.
17	J.M.	2.8/12	F	21.11.47.	-	I	+	+	-	-	-	9.5	3.0	5	Upper Respiratory Infection.	Well	4.2.48. No more fits - well.
18	J.G.	3.3/12	M	24.11.47.	-	I	+	-	-	-	N.D.	N.D.	N.D.	N.D.	Tuberculous Meningitis.	Well	Streptomycin treatment. 8.9.48. well: no fits.
19	M.S.	11 years	F	1.12.47.	-	I	++	-	-	-	-	9.9	4.0	-	Acute Haemorrhagic Nephritis.	Well	24.5.48. doing well: marked pseudo-papilloedema.
20	M.M.	6 years	F	5.12.47.	-	T	+++	+	-	-	N.D.	N.D.	N.D.	N.D.	Nephrosis. Pneumococcal Meningitis.	Died	No P.M.
21	J.S.	5/52	M	10.12.47.	-	C	+	+	-	-	N.D.	9.9	4.2	13	Pneumococcal Meningitis.	Died	Confirmed at P.M.
22	W.McC.	7.3/12	F	12.12.47.	-	I	+++	+	-	-	N.D.	9.6	2.5	2	Lobar Pneumonia.	Well	
23	J.G.	7/52	M	19.12.47.	-	T	++	+	-	-	N.D.	8.5	9.7	-	Ileocolitis.	Died	Confirmed at P.M.
24	D.S.	5.6/12	M	24.12.47.	+	C	-	-	-	-	N.D.	10.0	3.0	6	Epilepsy Mental Deficiency.	I.S.Q.	Hemiparesis. Aura.

Case Number	Initials	Age	Sex	Date of Admission	Previous Convulsion.	Type of Fit I, C or T.	Grade of Fever +, ++, +++	Acute Infection	Clinical Rickets	Clinical Tetany	X-ray	Serum Calcium	Plasma Phosphorus	Plasma Phosphatase	Diagnosis	Results	Comments-
25	R.R.	1 year	M	26.12.47.	-	I	++	+	-	-	-	9.8	4.5	11	Upper Respiratory Infection	Well	
26	R.B.	2.9/12	M	5.1.48.	-	I	-	+	-	-	N.D.	10.4	3.5	9.4	Upper Respiratory Infection	Well	
27	J.McC.	1 year	M	8.1.48.	-	I	+	+	-	-	N.D.	9.9	3.4	22.2	Upper Respiratory Infection	Well	Seen 23.2.48: well, no fits.
28	T.McL.	1.10/12	F	27.1.48.	-	I	+++	+	-	-	-	10.2	4.0	5.0	Upper Respiratory Infection	Well	
29	H.McK.	5.9/12	M	4.2.48.	+	C	-	-	-	-	-	10.0	4.2	5.0	Epilepsy	I.S.Q.	Dwarfed. Seen 31.5.48. No fits on phenobarbitone gr. 1/2 twice.daily.
30	V.J.	3 years	F	9.2.48.	+	C	-	-	-	-	N.D.	10.2	4.2	6.7	Epilepsy	I.S.Q.	19.7.48. Still has fits on phenobarbitone gr. 1/2 b.d: add phenytoin 0.05 g. twice. Still uncontrolled 16.8.48.
31	E.T.	5/12	F	9.2.48.	-	I	+++	+	-	-	-	9.6	4.0	8.4	Broncho-pneumonia	Well	Seen 28.2.48. Well.
32	E.C.	3.11/12	F	16.2.48.	+	C	-	-	-	-	-	9.9	3.7	13.5	Epilepsy	I.S.Q.	Seen 15.3.48. No fits on phenobarbitone gr. 1/2 twice.daily.
33	D.D.	1 year	F	18.2.48.	-	T	-	+	-	-	N.D.	N.D.	N.D.	N.D.	Nephrosis. Gastro-Enteritis	Died	P.M. Subacute nephritis and broncho-pneumonia.
34	J.R.	5/365	M	18.2.48.	-	T	-	+	-	-	N.D.	N.D.	N.D.	N.D.	Pneumococcal Meningitis	Died	Confirmed at P.M.
35	D.S.	5/12	M	18.2.48.	-	C	++	+	-	-	N.D.	11.5	3.3	5.3	Benign Lymphocytic Meningitis	Well	? Poliomyelitis.
36	S.W.	11 years	F	19.2.48.	+	C	-	-	-	-	N.D.	9.1	4.6	12	Epilepsy	I.S.Q.	Seen 8.7.48. No fits on phenobarbitone gr. 1/2 twice. daily.
37	B.L.	4½/12	M	20.2.48.	-	I	+++	+	+	+	N.D.	5.1	10.0	46.8	Broncho-pneumonia Tetany	Died	Chvostek ++: Craniotabes ++ with bossing.

Case Number	Initials	Age	Sex	Date of Admission	Previous Convulsion	Type of Fit I, C or T.	Grade of Fever +, ++, +++	Acute Infection	Clinical Rickets	Clinical Tetany	X-ray	Serum Calcium	Plasma Phosphorus	Plasma Phosphatase	Diagnosis	Results	Comments
38	T.W.	5 years	M	22.2.48.	-	I	+++	+	-	-	N.D.	10.6	3.8	-	Benign Lymphocytic Meningitis	Well	
39	M. McI.	9/12	F	23.2.48.	+	C	-	-	-	-	N.D.	10.7	5.4	18.4	Mental Deficiency	I.S.Q.	Frequent fits on phenobarbitone gr. 1/4 twice.daily. (17.5.48.)
40	W.K.	2/12	M	25.2.48.	-	T	-	+	-	-	N.D.	N.D.	N.D.	N.D.	Pyloric stenosis. Gastro-enteritis.	Died	Confirmed at P.M.
41	H.McL.	9 years	F	25.2.48.	+	C	-	-	-	-	N.D.	9.8	4.5	9.7	Epilepsy	I.S.Q.	Phenobarbitone increased to gr. 1 b.d. on 30.8.48.
42	J.G.	8/52	M	27.2.48.	-	I	-	-	-	-	N.D.	10.0	6.4	4.0	Convulsion	Well	Re-admitted 14.3.48. with gastro-enteritis and died: no more fits.
43	A.H.	5½/12	F	28.2.48.	-	I	++	-	-	-	N.D.	10.0	3.3	-	Tuberculous Meningitis	Died	
44	M.G.	1.5/12	F	1.3.48.	-	I	+	+	-	-	N.D.	N.D.	N.D.	N.D.	Microcephaly. Broncho-pneumonia.	Died	
45	J.A.	6.3/12	F	10.3.48.	-	I	+++	+	-	-	N.D.	11.3	3.2	3.2	Acute Tonsillitis	Well	Seen 3.5.48: well.
46	J.McC.	3.11/12	M	11.3.48.	-	I	-	+	-	-	N.D.	9.4	3.4	4.1	Upper Respiratory Infection	Well	
47	S.McK.	10/12	M	24.3.48.	-	I	+++	+	-	-	N.D.	10.2	4.4	4.9	Measles. Mongol.	Transf.	
48	R.B.	6 years	M	24.3.48.	-	C	-	+	-	-	N.D.	9.4	3.5	3.0	Encephalitis	Well	13.8.48: no fits.
49	J.T.	2 years	M	24.3.48.	+	C	+	+	+	-	-	9.7	1.9	18.7	Mental Deficiency Otitis Media Rickets.	Imp.	
50	J.McL.	6 years	F	1.4.48.	+	C	-	-	-	-	N.D.	9.3	3.7	8.3	Epilepsy Mental Deficiency.	I.S.Q.	9.8.48: no fits on phenobarbitone gr. 1/2 b.d.

Case Number	Initials	Age	Sex	Date of Admission	Previous Convulsion	Type of Fit I, C or T	Grade of Fever +, ++, +++	Acute Infection	Clinical Rickets	Clinical Tetany	X-ray	Serum Calcium	Plasma Phosphorus	Plasma Phosphatase	Diagnosis	Results	Comments
51	E.McK.	1.9/12	F	4.4.48.	-	T	+++	-	-	-	N.D.	N.D.	N.D.	N.D.	Tuberculous Meningitis	Died	Confirmed at P.M.
52	G.B.	1/52	M	9.4.48.	-	C	+	-	-	+	N.D.	9.4	8.0	-	Convulsions	Well	Seen 23.4.48: well. (Cnvostek +ve)
53	F.L.	9/12	F	9.4.48.	-	I	+++	+	-	-	N.D.	N.D.	N.D.	N.D.	Measles	Transf.	Transient post-convulsive hemiparesis.
54	E.McK.	2.9/12	F	21.4.48.	-	I	+	+	-	-	-	10.0	3.4	4.3	Gastro-enteritis	Well	
55	I.M.	9/12	F	7.5.48.	-	C	++	-	-	-	N.D.	10.7	3.4	9.9	Tuberculous Meningitis	Died	Confirmed at P.M.
56	R.I.	7/12	F	18.5.48.	-	T	+++	+	-	-	N.D.	N.D.	N.D.	N.D.	Gastro-enteritis	Died	Confirmed at P.M.
57	E.McC.	2.3/12	F	18.5.48.	-	T	+	-	-	-	N.D.	N.D.	N.D.	N.D.	Tuberculous Meningitis	Died	No P.M.
58	R.McL.	1.7/12	M	18.5.48.	-	I	-	+	-	-	N.D.	10.3	4.2	8	Upper Respiratory Infection	Well	
59	W.I.	1 year	M	21.5.48.	-	I	++	-	-	-	N.D.	N.D.	N.D.	N.D.	Tuberculous Meningitis	Imp.	Streptomycin treatment: 13.9.48. No further fits.
60	C.T.	3.7/12	F	25.5.48.	-	I	+	+	-	-	N.D.	9.8	3.4	9.8	Acute Tonsillitis	Well	
61	D.C.	10/52	M	28.5.48.	-	C	+++	+	-	-	N.D.	10.1	3.1	7.8	Broncho-pneumonia	Well	Seen 25.8.48. No more fits.
62	T.P.	1.3/12	M	13.6.48.	-	I	+++	+	-	-	N.D.	10.1	3.2	6.0	Upper Respiratory Infection	Well	Transient post-convulsive hemiparesis (left).
63	E.T.	1.1/12	F	13.6.48.	+	C	-	-	-	-	-	9.9	3.6	11.3	Convulsions	Well	No more fits 3.9.48. No sedative.
64	D.R.	10/365	M	23.6.48.	-	C	-	+	-	+	N.D.	14.5	5.5	4.5	Septicaemia. Porencephaly.	Died	Confirmed at P.M.

APPENDIX II

BIOCHEMICAL METHODS

Blood was collected in a dry sterile syringe with care to avoid haemolysis and immediately transferred to two specially cleaned centrifuge tubes to one of which was added a drop of a saturated solution of sodium oxalate. Approximately 5 ccs. were added to each tube. The absence of satisfactory micro-methods for calcium and phosphorus made this large amount of blood necessary. In only one or two cases was a determination upon smaller amounts enforced by difficulty in obtaining the full amount of blood. The estimations were always begun within half an hour of the withdrawal of blood and carried to a stage at which they could be safely left.

Serum Calcium

Nearly all calcium determinations depend upon the precipitation of calcium as the very insoluble oxalate, the subsequent procedure being either gravimetric, gasometric or volumetric (Peters and van Slyke, 1932). In clinical work the method of Kramer and Tisdall (1921) is almost always employed and was the method employed in the large series to determine normal and abnormal values in children (Howland and Kramer, 1921, Kramer, Tisdall and Howland, 1921). This method, as described by Harrison (1947) was employed. 2 ccs. of serum

was/

was used in almost every case. In one or two cases a smaller amount was used but these did not include any of the low results. The precipitation was allowed to proceed overnight in most cases and the estimation was in no case proceded with before two or three hours had elapsed. Technique was checked by serial estimations on the same specimen and with good agreement.

Inorganic Phosphate

Colorimetric methods are the most practicable in the absence of a micro-balance (Peters and van Slyke, 1932). These depend mostly upon the formation of phosphomolybdate and its reduction to an estimable blue colour. Various reducing agents are employed in different methods and the resultant colours vary in density and rate of fading. To gain added accuracy it was decided to use a photoelectric colorimeter and for this purpose a certain modification in the method might be necessary. It was decided to try the method in use at the Biochemical Laboratory at this hospital. This method (that of Kuttner and Cohen) uses a fresh solution of stannous chloride as reducing agent and is described in detail by Hawk and Bergheim (1938). The method has the advantage of producing an intense colour but while this is an advantage for use with a colorimeter of the Dubosc type it is not so when used in the more sensitive photoelectric colorimeter.

Various standards were made up and serial readings were made/

made every two minutes in the photoelectric colorimeter with the light switched off between readings. This showed a rapid rate of fading with a considerable fall in the reading after only two minutes and a fall to 50% within half an hour. This was even greater if the solution was exposed to a strong light all the time. The method was therefore quite unsuitable for use with this instrument. The method of Briggs (1922) as described by Harrison (1947) was then tried and this method which uses hydroquinone and sodium sulphite as reducing agents produces a very much less intense colour but well suited to the photoelectric colorimeter. The fading rate was determined by the same method and found to be negligible even after one hour. The rate of development of the colour was also studied to determine how precisely the standing for thirty minutes recommended had to be adhered to. The colour was found to develop its maximum in twenty minutes thus allowing some considerable grace. No dilution of the resulting colour was necessary even for the higher values.

The instrument was then calibrated with a series of known solutions of phosphate. Various filters were tried to find the one that would give the nearest to the ideal calibration, that is the nearest to a linear correlation between dilution and distance from the point of light. An orange filter was used at first but later changed to Ilford Tricolour-red as recommended by King (1947). The calibration was

frequently checked and a standard always employed. Technique was checked by serial estimations on discarded Blood-Bank plasma with good agreement.

Alkaline Phosphatase

The method of King and Armstrong as described by Harrison (1947) and modified for use with a photoelectric colorimeter by King (1947). The development of the colour was studied in the same way as that of the phosphate estimation and no fading was discovered within the time of the estimation. The maximum stable colour was not found to appear at 15 minutes incubation and there was a small but discernible intensification of the colour up to 25 minutes which thereafter remained constant. Accordingly the final incubation was increased to thirty minutes thus fitting nicely with the phosphate estimation. Adequate agreement with serial estimations was obtained but it must be confessed that the agreement was never so exact as with the other two estimations and I am not wholly satisfied with the precision of the method at least in my hands.

A P P E N D I X III

BIBLIOGRAPHY

The Bibliography is divided into two sections for convenience. The first section subserves the first part of the review of the literature entitled "The Historical Background". The second section contains all the other references quoted.

This roughly separates papers of the twentieth century from those of the past.

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A P P E N D I X IV

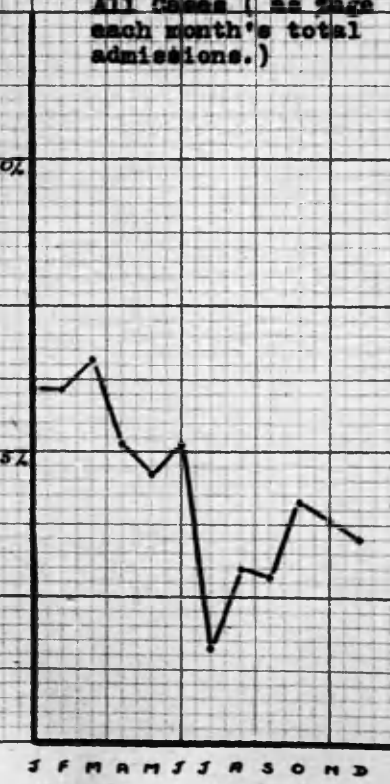
PLATES I TO XXII

MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1922 - 1926.

All Cases (actual figures)

MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1922 - 1926.

All Cases (as %age of each month's total admissions.)



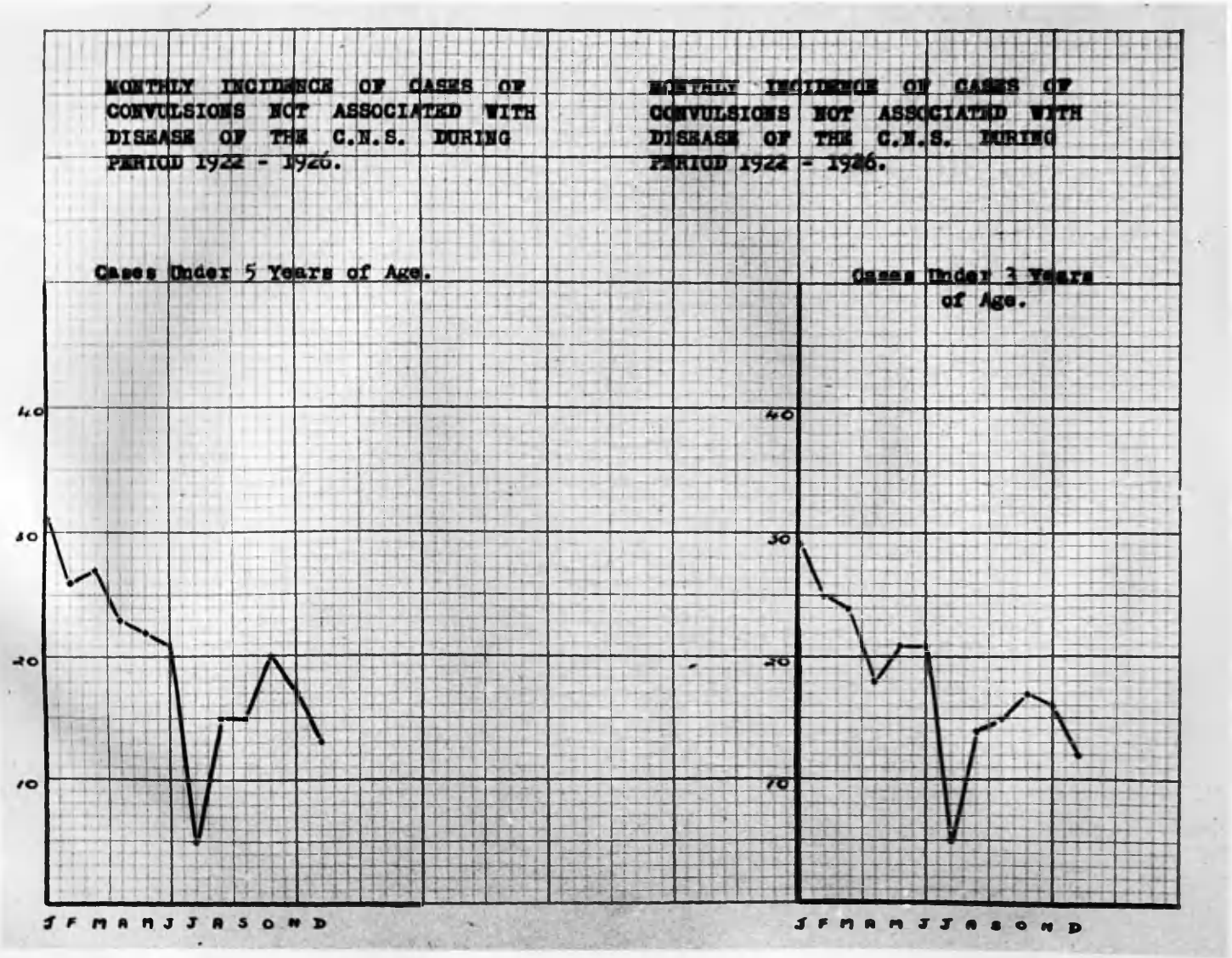
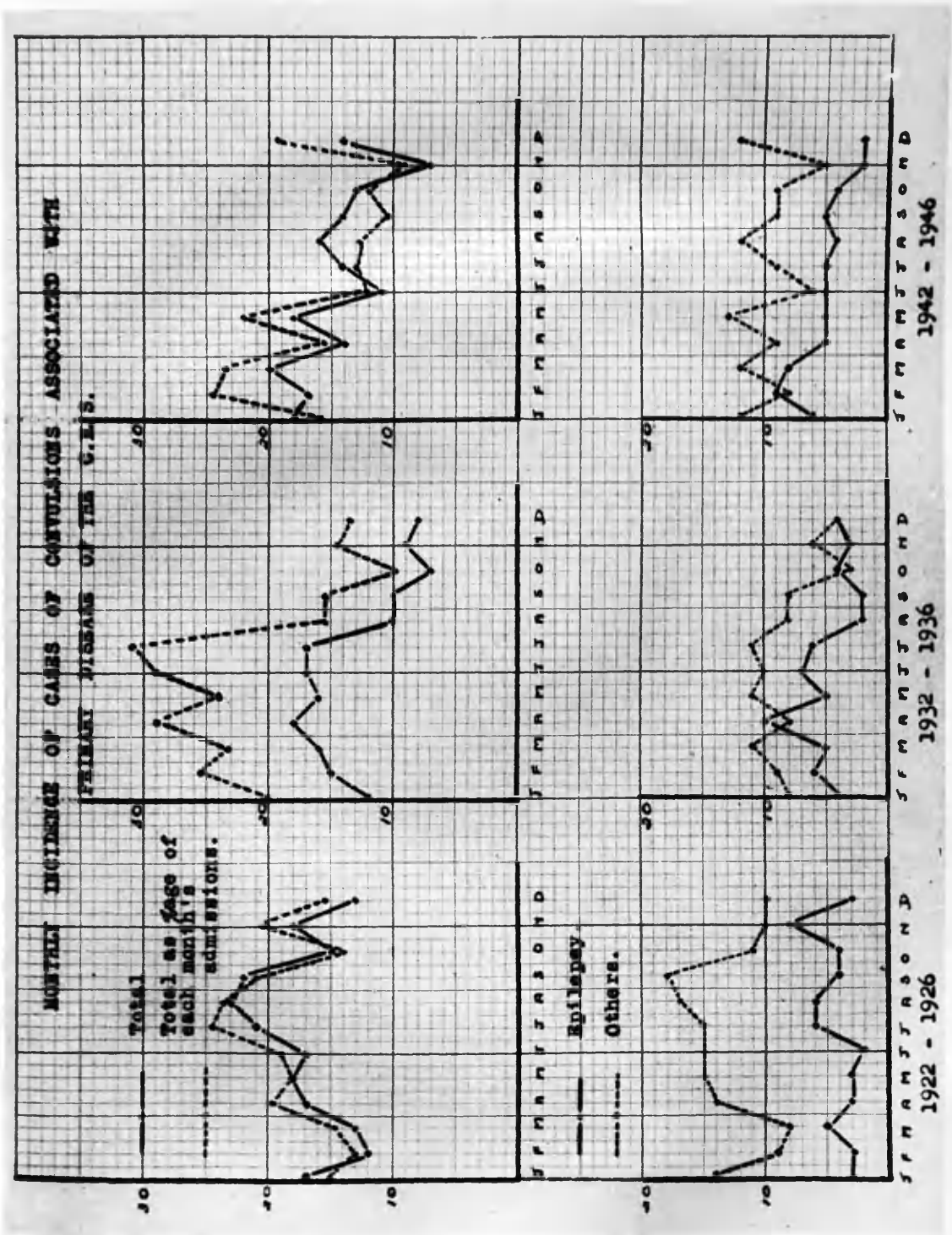
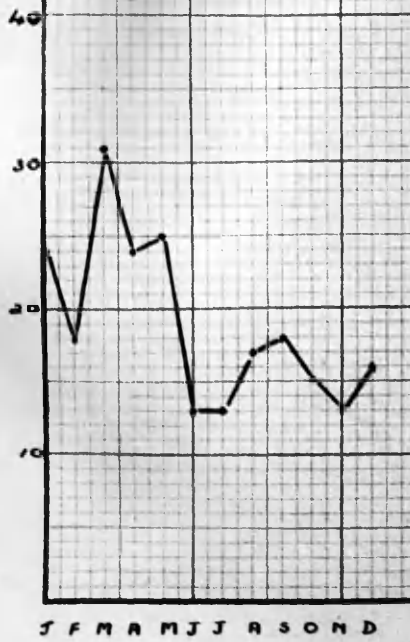

MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1922 - 1926.
Cases Under 5 Years of Age.
40
30
20
10
J F M A M J J A S O N D
MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1922 - 1926.
Cases Under 3 Years of Age.
40
30
20
10
J F M A M J J A S O N D

PLATE III


MONTHLY INCIDENCE OF CASES OF CONVULSIONS ASSOCIATED WITH PRIMARY DISEASE OF THE C.N.S.
Total
Total as % age of each month's admissions.
Epilepsy.
Others.
J F M A M J J A S O N D
1922 - 1926
1932 - 1936
1942 - 1946

MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1932 - 1936.

All Cases (actual figures)



MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1932 - 1936.

All Cases (as %age of each month's total admissions.)

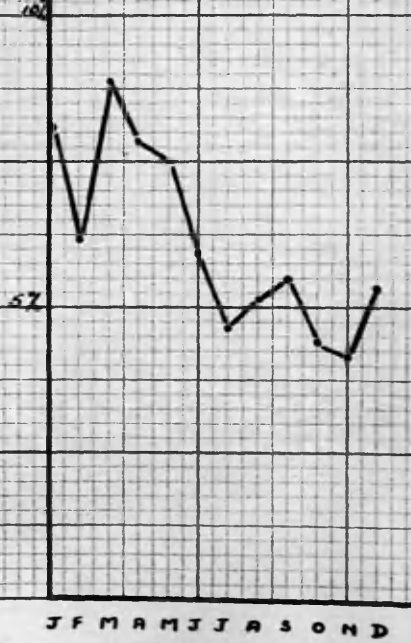
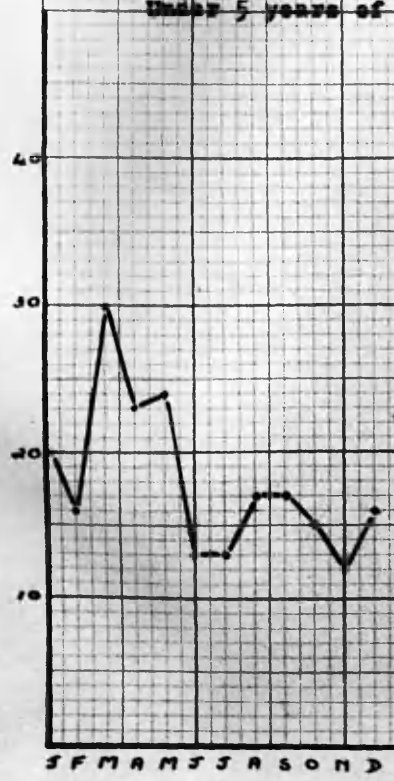


PLATE V

MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1932 - 1936.

Under 5 years of age.



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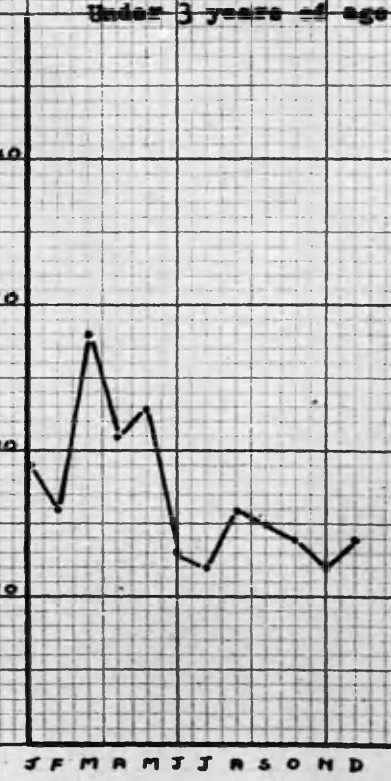
Under 3 years of age.



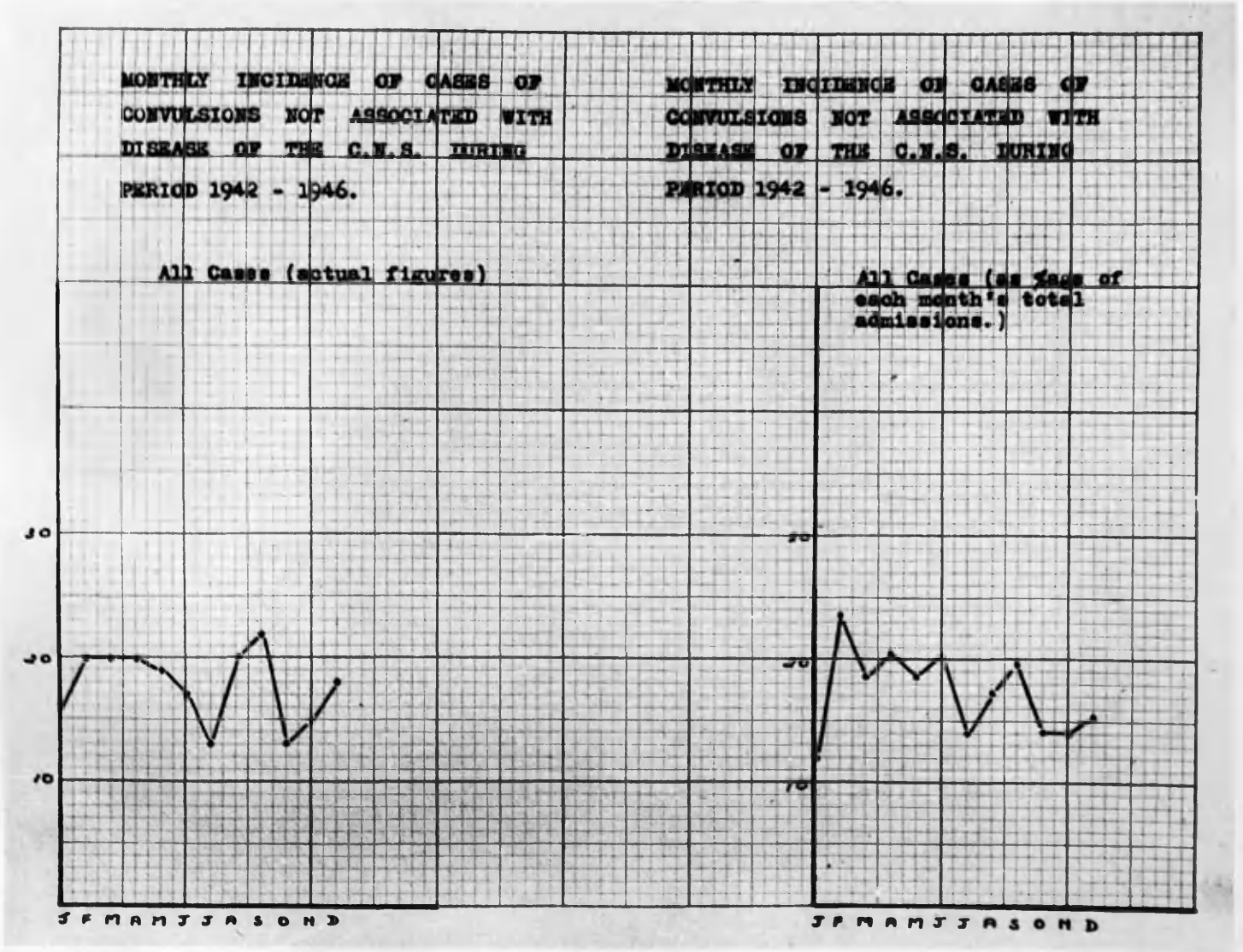
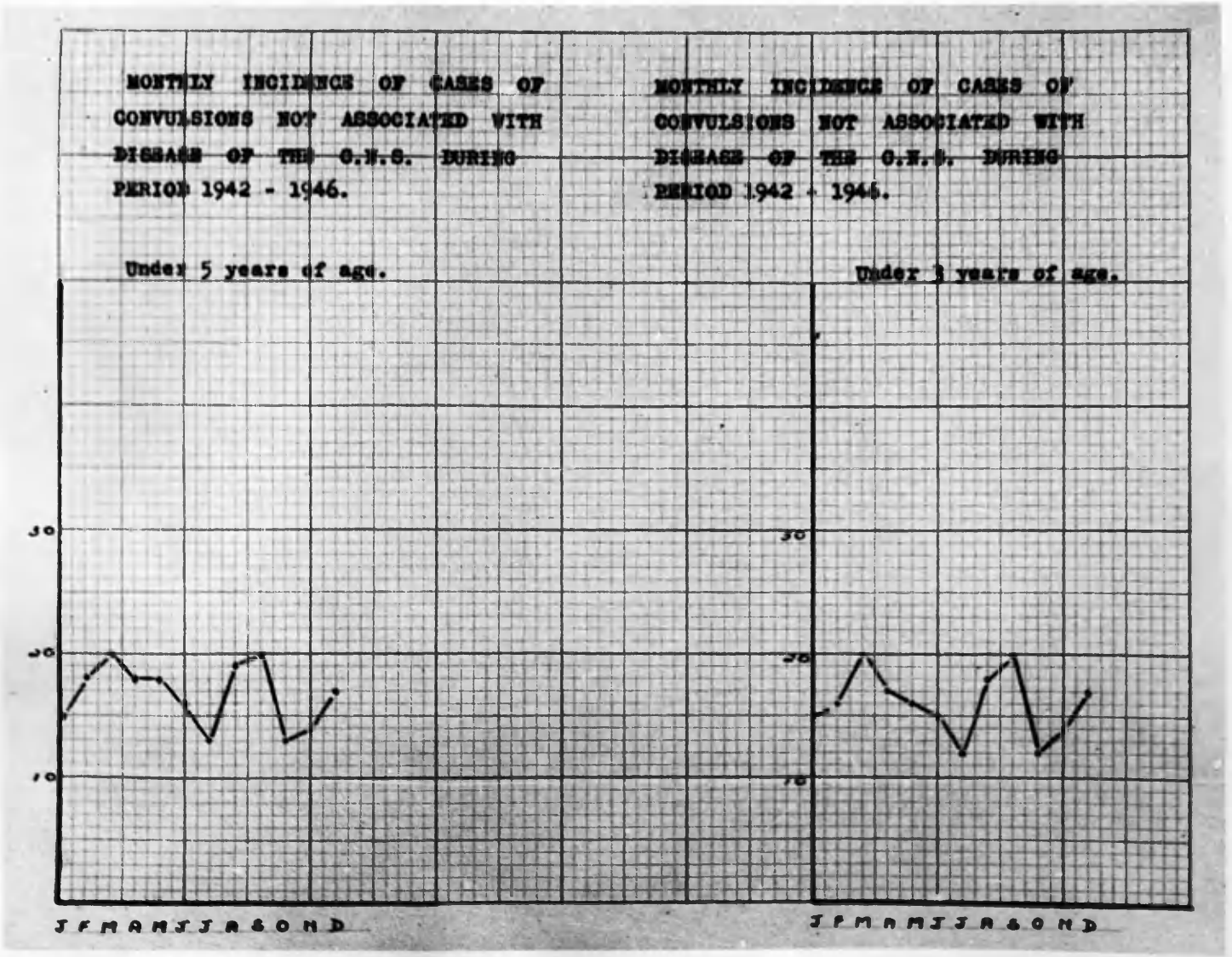

MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1942 - 1946.
All Cases (actual figures)
30
20
10
J F M A M J J A S O N D
MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1942 - 1946.
All Cases (as %age of each month's total admissions.)
30
20
10
J F M A M J J A S O N D

PLATE VI


MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1942 - 1946.
Under 5 years of age.
30
20
10
J F M A M J J A S O N D
MONTHLY INCIDENCE OF CASES OF CONVULSIONS NOT ASSOCIATED WITH DISEASE OF THE C.N.S. DURING PERIOD 1942 - 1946.
Under 3 years of age.
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J F M A M J J A S O N D

PLATE VII

PLATE VIII

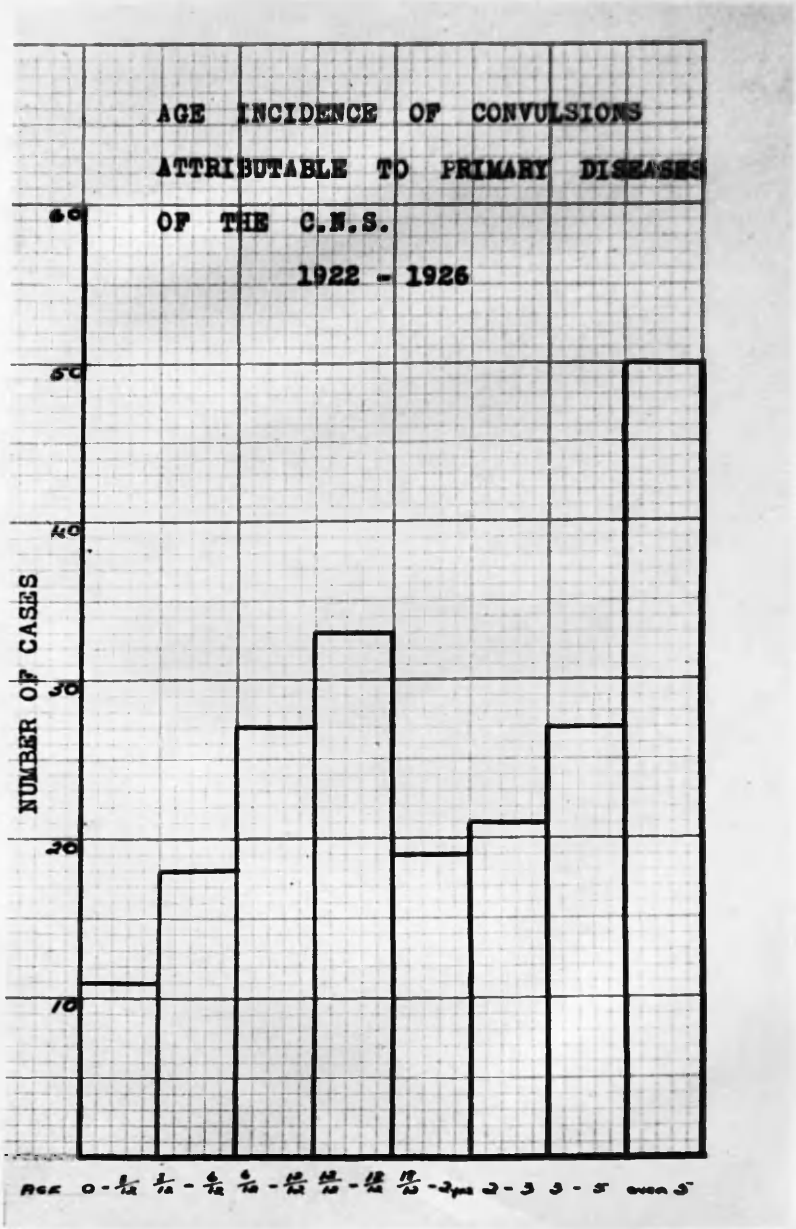

AGE INCIDENCE OF CONVULSIONS
ATTRIBUTABLE TO PRIMARY DISEASES
OF THE C.N.S.
1922 - 1926
NUMBER OF CASES
60
50
40
30
20
10
Age 0 - 3/12 3/12 - 6/12 6/12 - 9/12 9/12 - 12/12 12/12 - 18/12 18/12 - 3yrs 2 - 3 3 - 5 over 5

PLATE IX

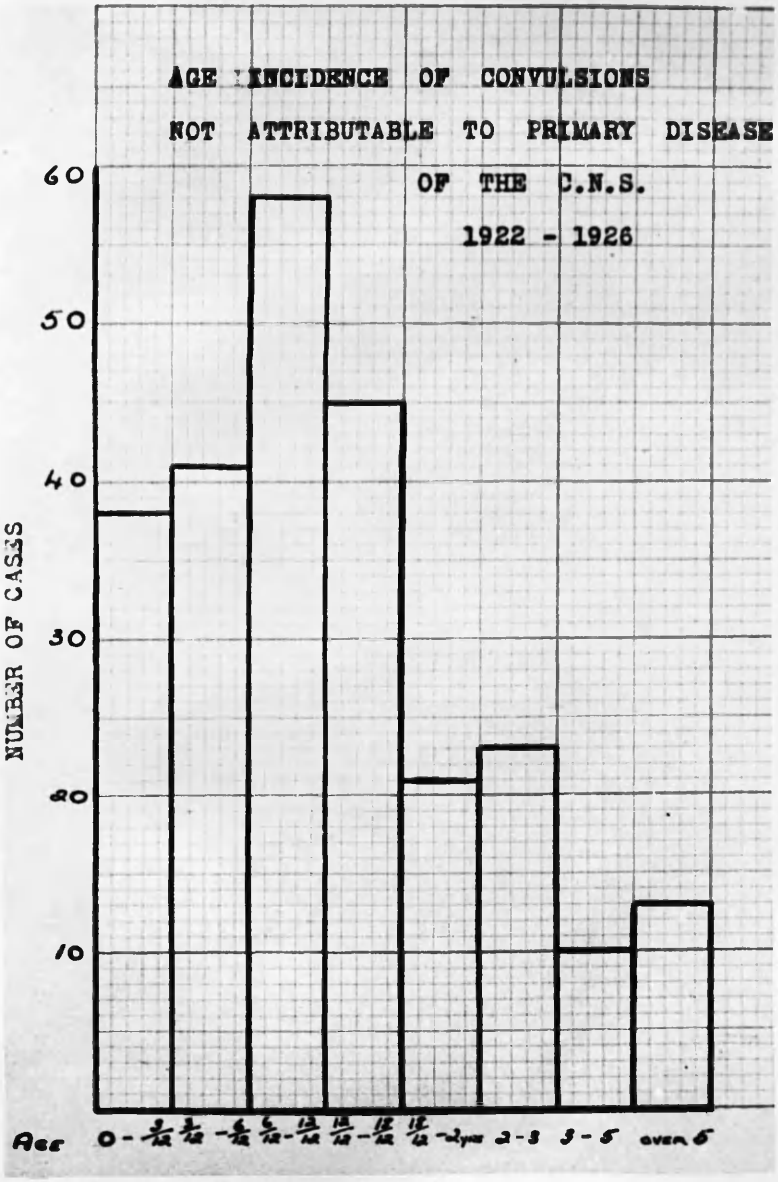

AGE INCIDENCE OF CONVULSIONS
NOT ATTRIBUTABLE TO PRIMARY DISEASE
OF THE C.N.S.
1922 - 1926
NUMBER OF CASES
60
50
40
30
20
10
Age
0 - 2/12
2/12 - 6/12
6/12 - 12/12
12/12 - 18/12
18/12 - 2yrs
2 - 3
3 - 5
over 5

PLATE X

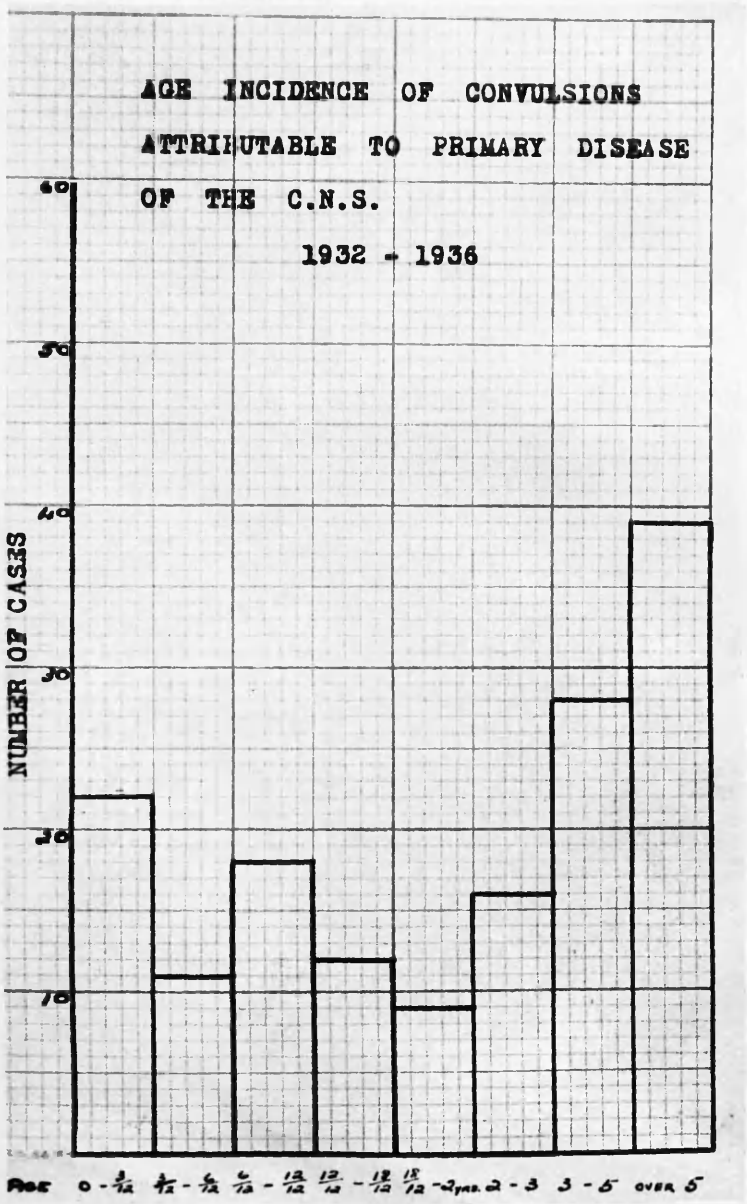

AGE INCIDENCE OF CONVULSIONS
ATTRIBUTABLE TO PRIMARY DISEASE
OF THE C.N.S.
1932 - 1936
NUMBER OF CASES
40
30
20
10
AGE
0 - 3/12
3/12 - 6/12
6/12 - 12/12
12/12 - 18/12
18/12 - 2yrs.
2 - 3
3 - 5
over 5

PLATE XI

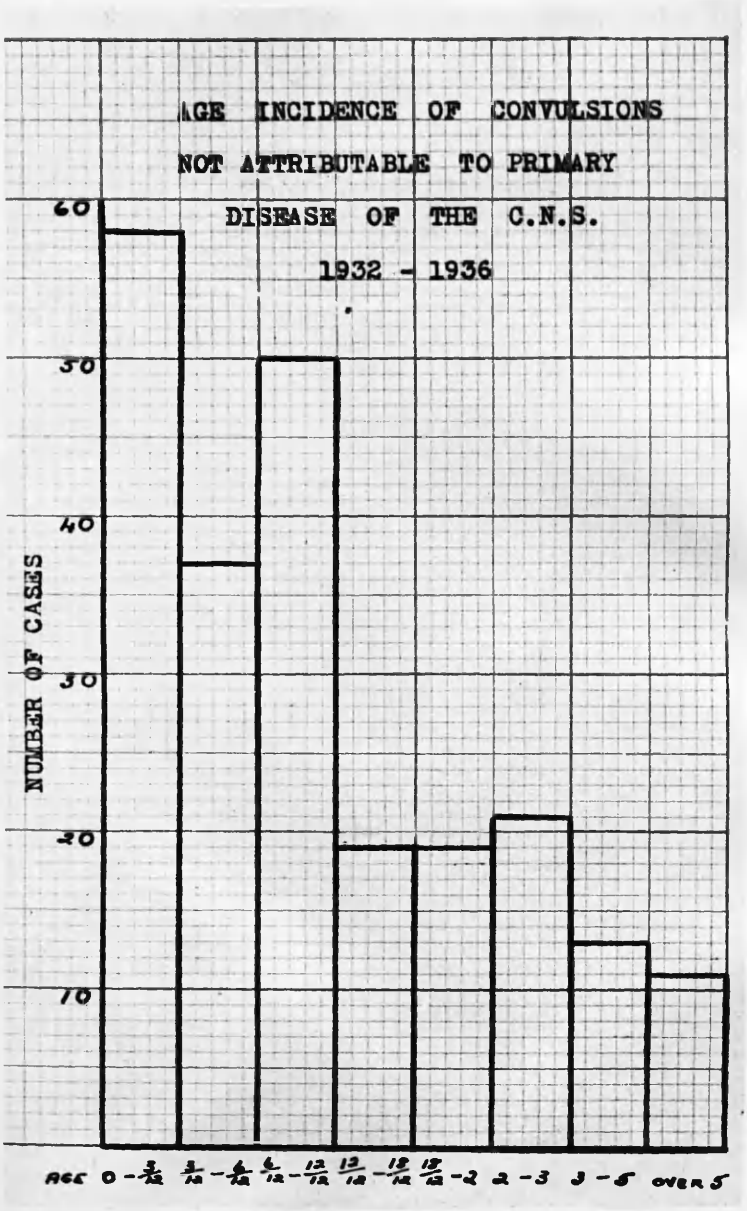

AGE INCIDENCE OF CONVULSIONS
NOT ATTRIBUTABLE TO PRIMARY
DISEASE OF THE C.N.S.
1932 - 1936
NUMBER OF CASES
60
50
40
30
20
10
AGE 0 - 3/12 3/12 - 6/12 6/12 - 12/12 12/12 - 18/12 18/12 - 2 2 - 3 3 - 5 OVER 5

PLATE XII

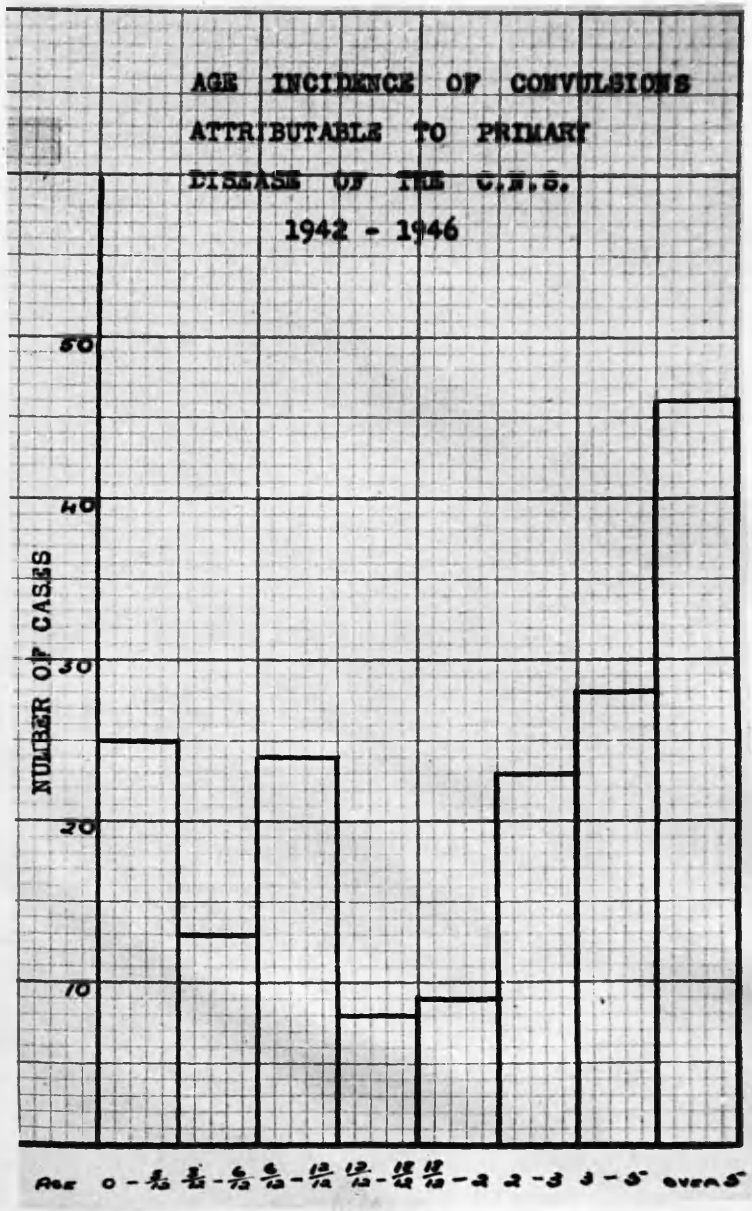

AGE INCIDENCE OF CONVULSIONS
ATTRIBUTABLE TO PRIMARY
DISEASE OF THE C.N.S.
1942 - 1946
NUMBER OF CASES
50
40
30
20
10
Age 0 - 3/12 3/12 - 6/12 6/12 - 12/12 12/12 - 18/12 18/12 - 2 2 - 3 3 - 5 over 5

PLATE XIII

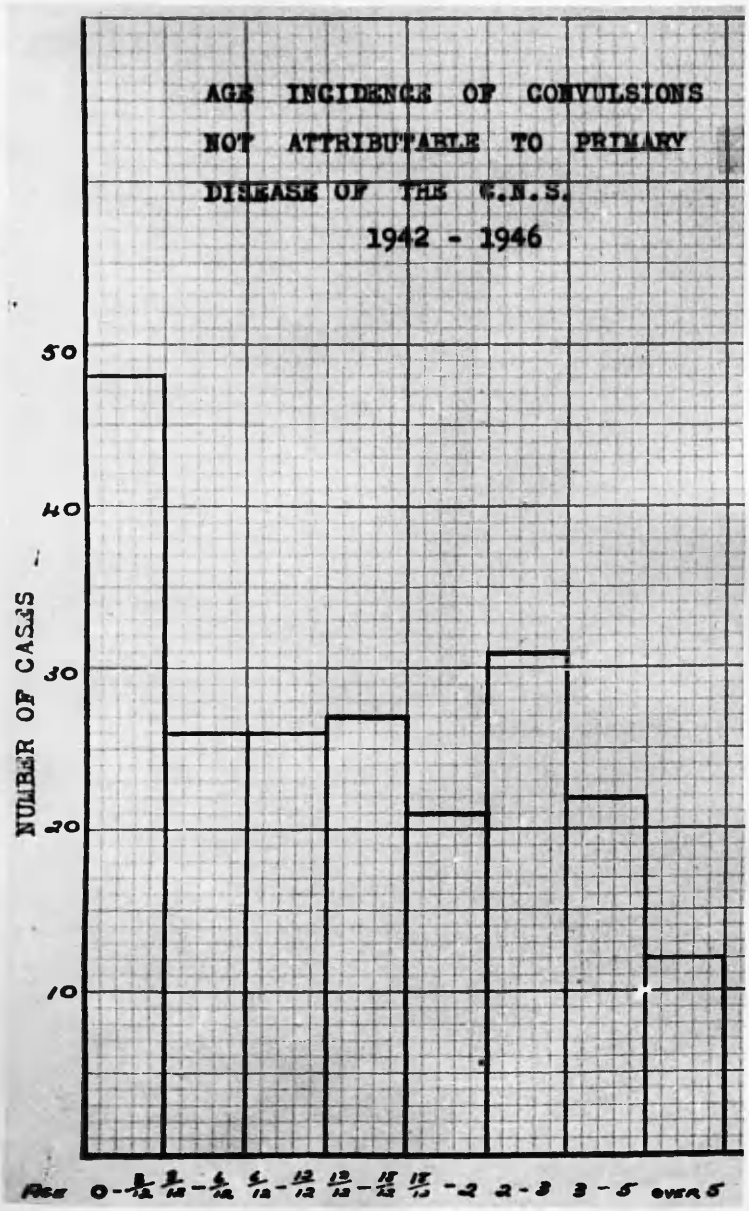
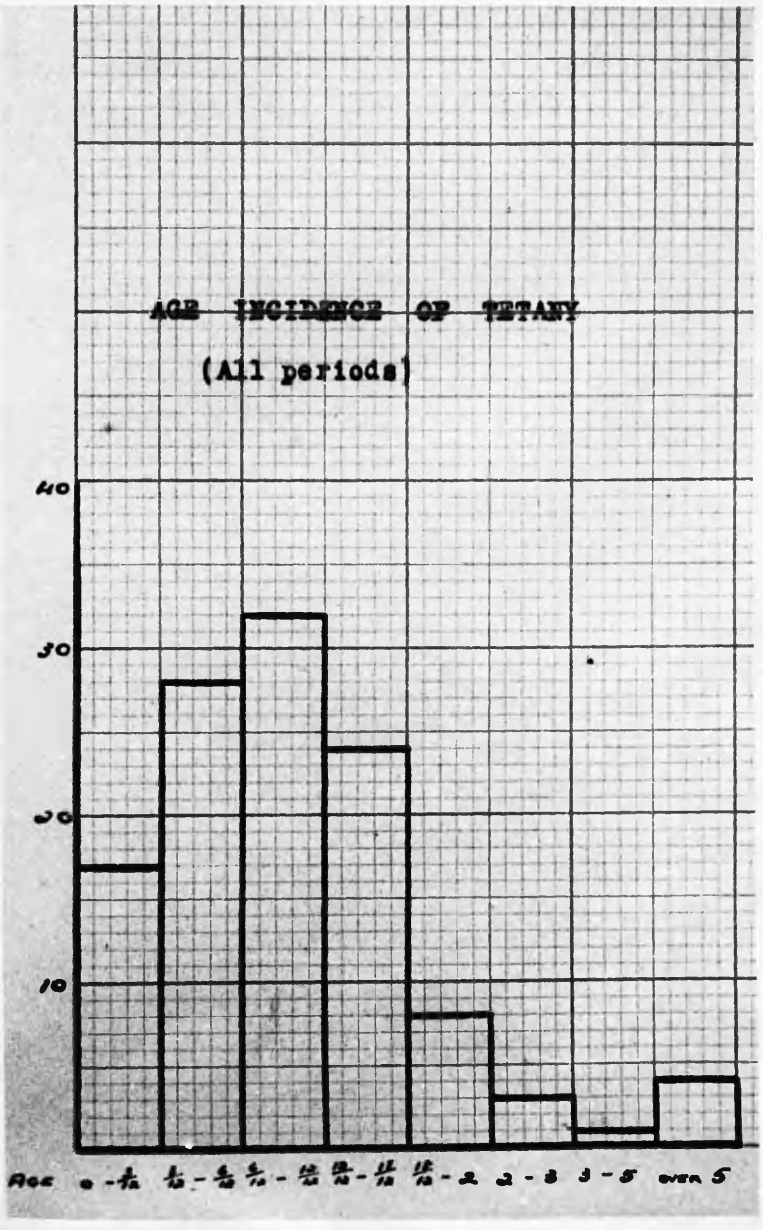

AGE INCIDENCE OF CONVULSIONS
NOT ATTRIBUTABLE TO PRIMARY
DISEASE OF THE C.N.S.
1942 - 1946
NUMBER OF CASES
50
40
30
20
10
AGE
0 - 3/12
3/12 - 6/12
6/12 - 12/12
12/12 - 18/12
18/12 - 2
2 - 3
3 - 5
OVER 5

PLATE XIV


AGE INCIDENCE OF TETANY
(All periods)
40
30
20
10
Age 0 - 1/4 1/4 - 1/2 1/2 - 3/4 3/4 - 1 1 - 2 2 - 3 3 - 5 over 5

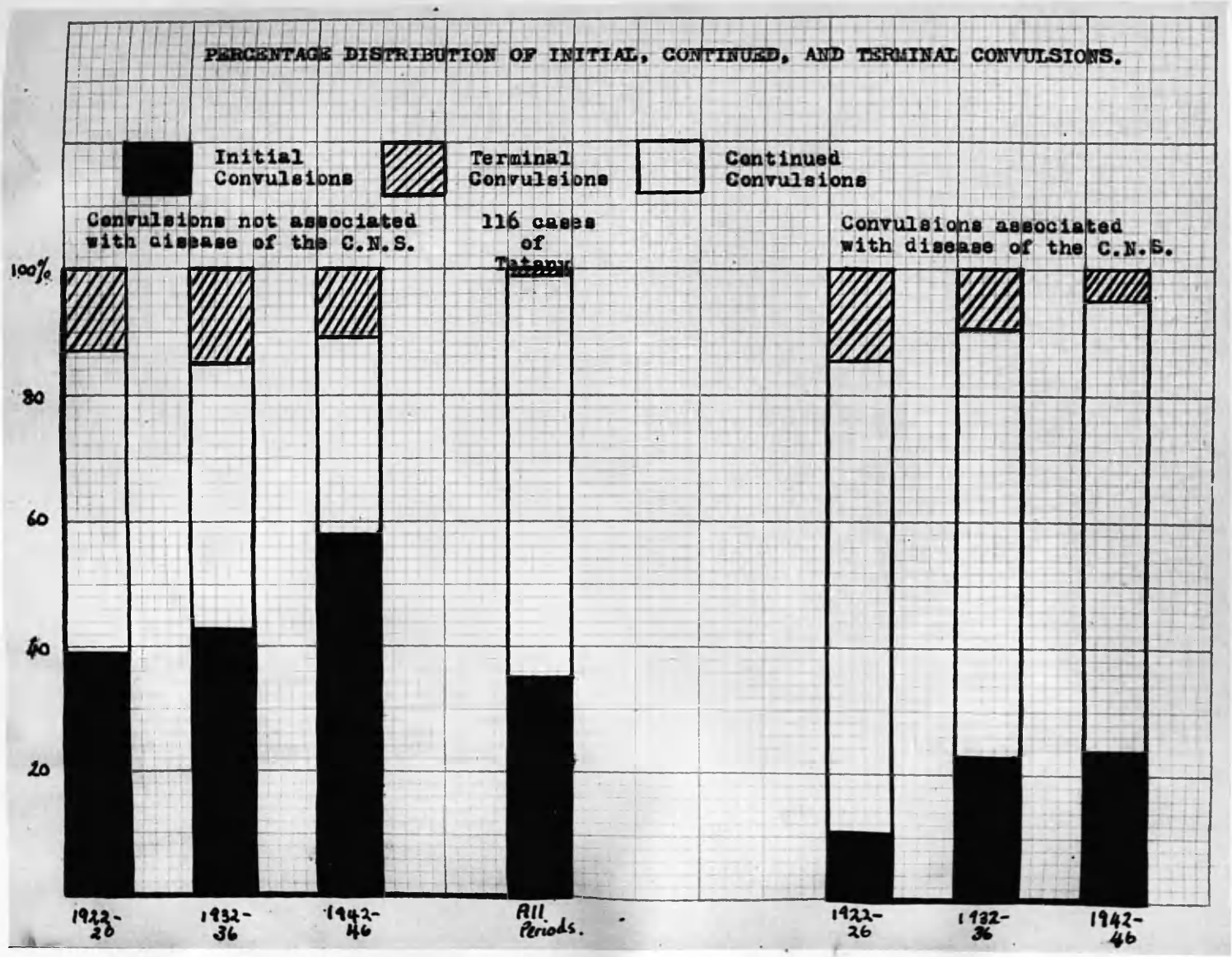

PERCENTAGE DISTRIBUTION OF INITIAL, CONTINUED, AND TERMINAL CONVULSIONS.
Initial Convulsions
Terminal Convulsions
Continued Convulsions
Convulsions not associated with disease of the C.N.S.
116 cases of Tetany
Convulsions associated with disease of the C.N.S.
100%
80
60
40
20
1922-26
1932-36
1942-46
All Periods.
1922-26
1932-36
1942-46

PLATE XV

PLATE XVI

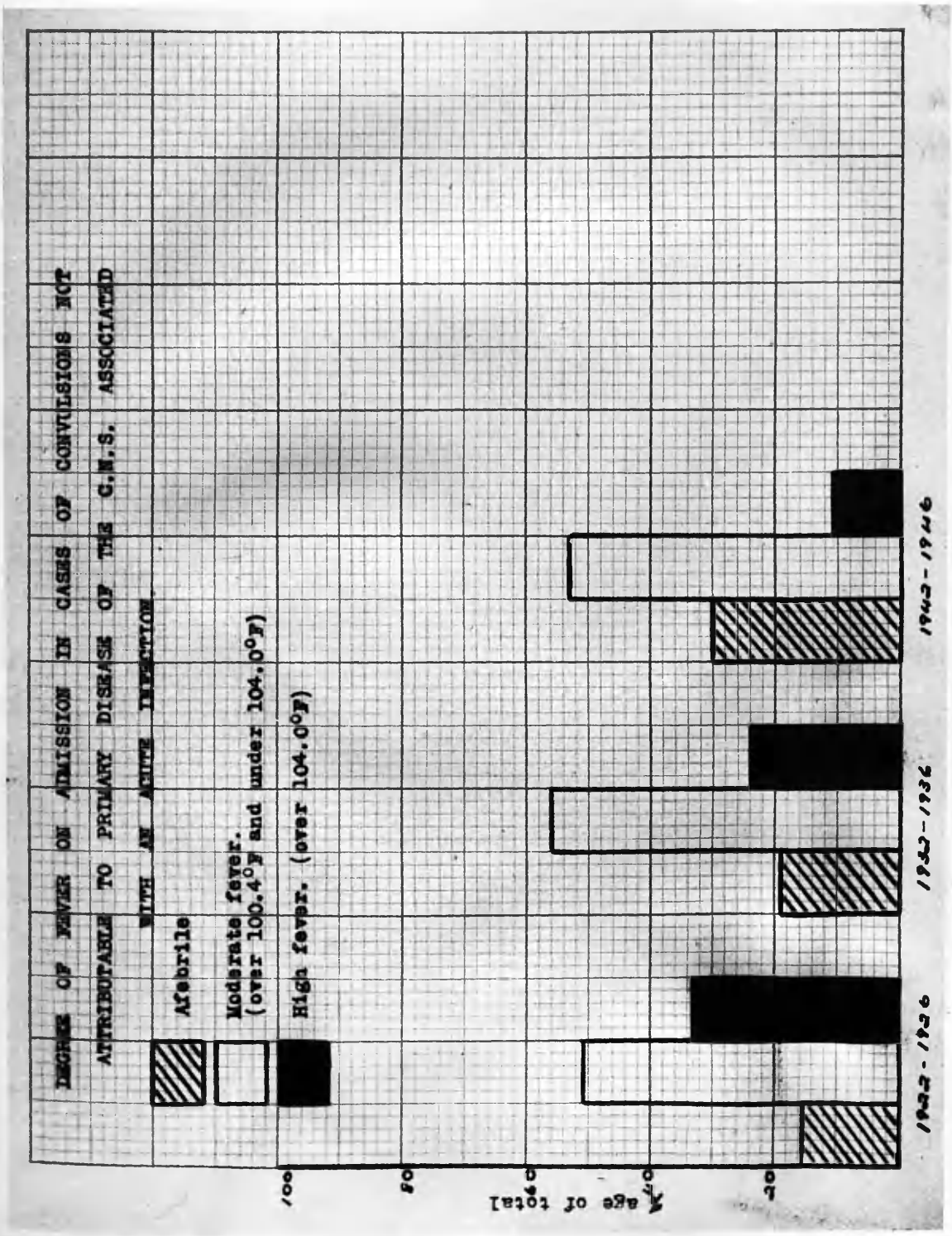
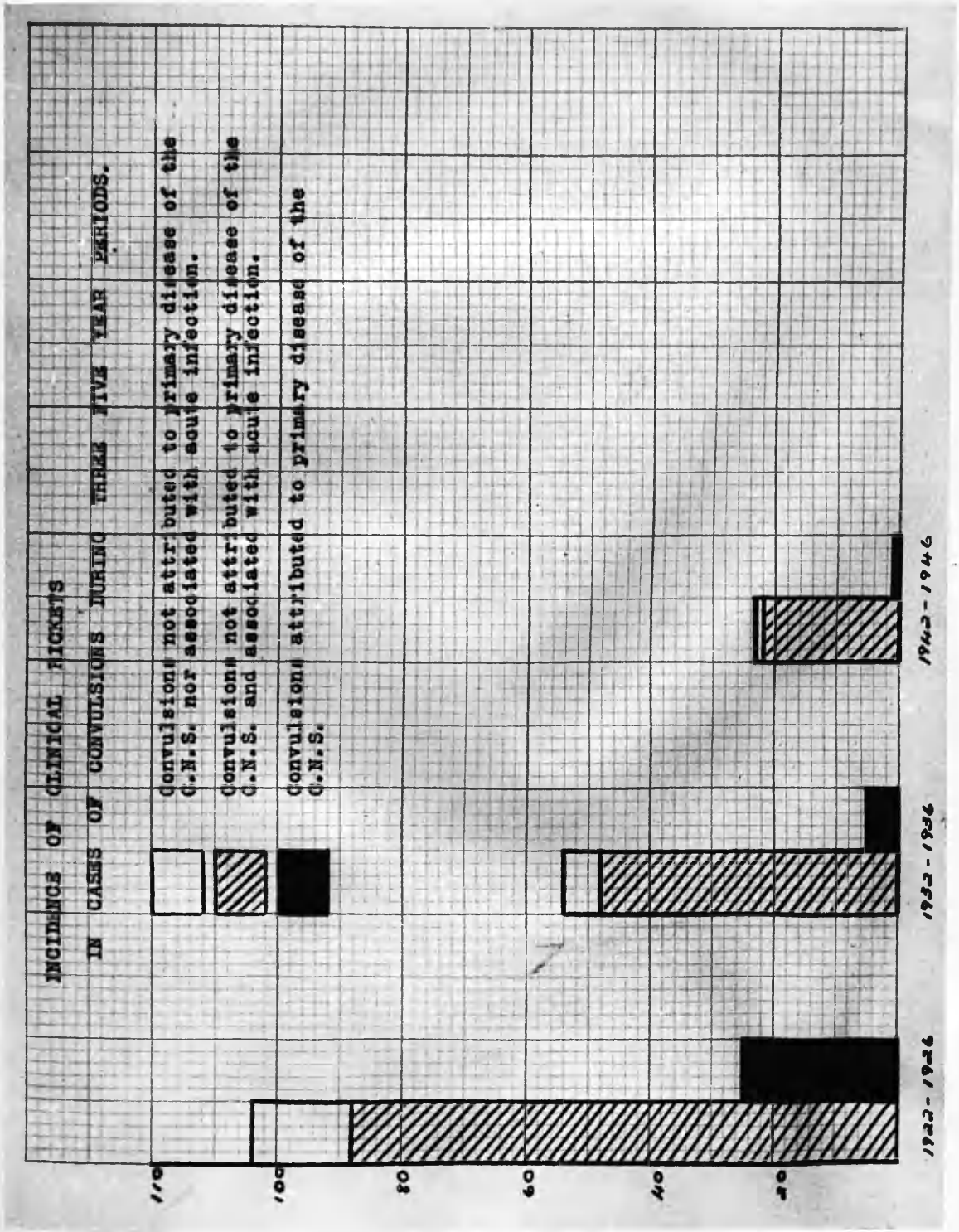

DEGREE OF FEVER ON ADMISSION IN CASES OF CONVULSIONS NOT ATTRIBUTABLE TO PRIMARY DISEASE OF THE C.N.S. ASSOCIATED WITH AN ACUTE INFECTION
Afebrile
Moderate fever. (over 100.4°F and under 104.0°F)
High fever. (over 104.0°F)
% age of total
100
50
0
50
1932 - 1939
1940 - 1946

PLATE XVII


INCIDENCE OF CLINICAL RICKETS
IN CASES OF CONVULSIONS DURING THREE FIVE YEAR PERIODS.
Convulsions not attributed to primary disease of the C.N.S. nor associated with acute infection.
Convulsions not attributed to primary disease of the C.N.S. and associated with acute infection.
Convulsions attributed to primary disease of the C.N.S.
110
100
80
60
40
20
1921-1926
1931-1936
1941-1946

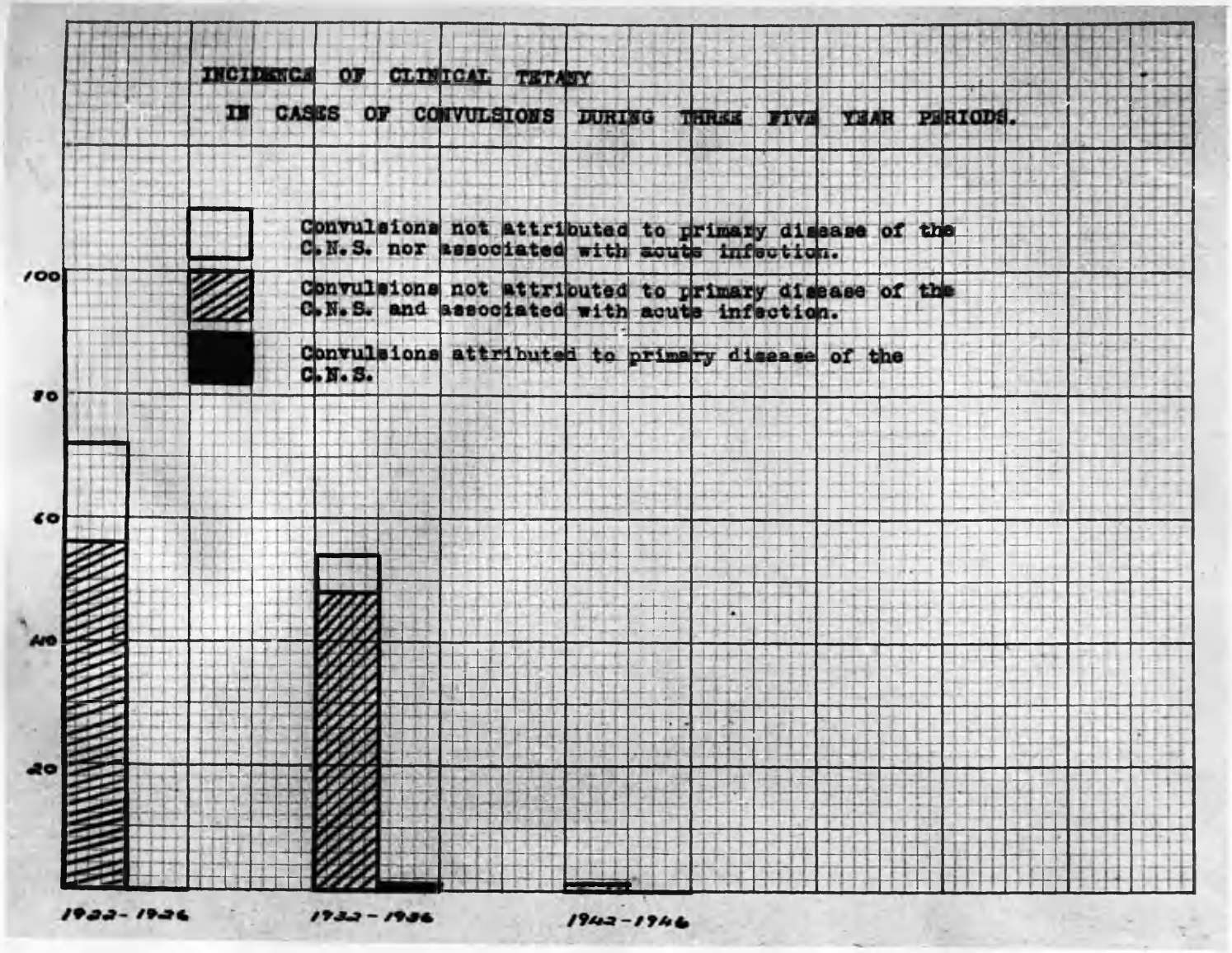
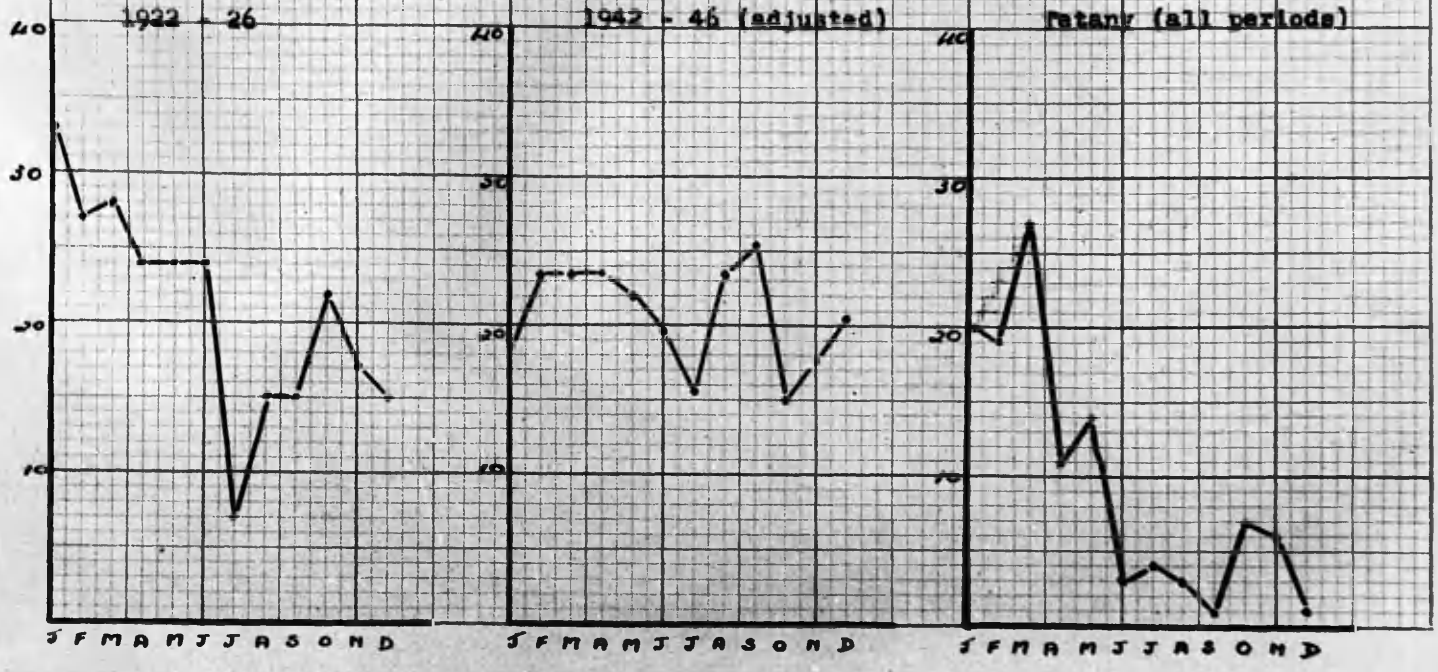

INCIDENCE OF CLINICAL TETANY
IN CASES OF CONVULSIONS DURING THREE FIVE YEAR PERIODS.
Convulsions not attributed to primary disease of the C.N.S. nor associated with acute infection.
Convulsions not attributed to primary disease of the C.N.S. and associated with acute infection.
Convulsions attributed to primary disease of the C.N.S.
100
80
60
40
20
1922-1926
1932-1936
1942-1946

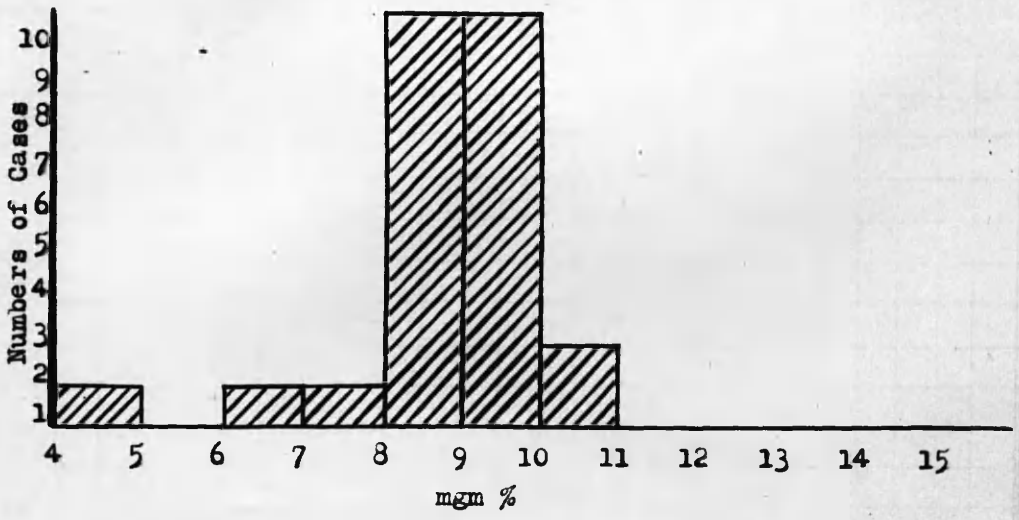
PLATE XVIII

PLATE XIX

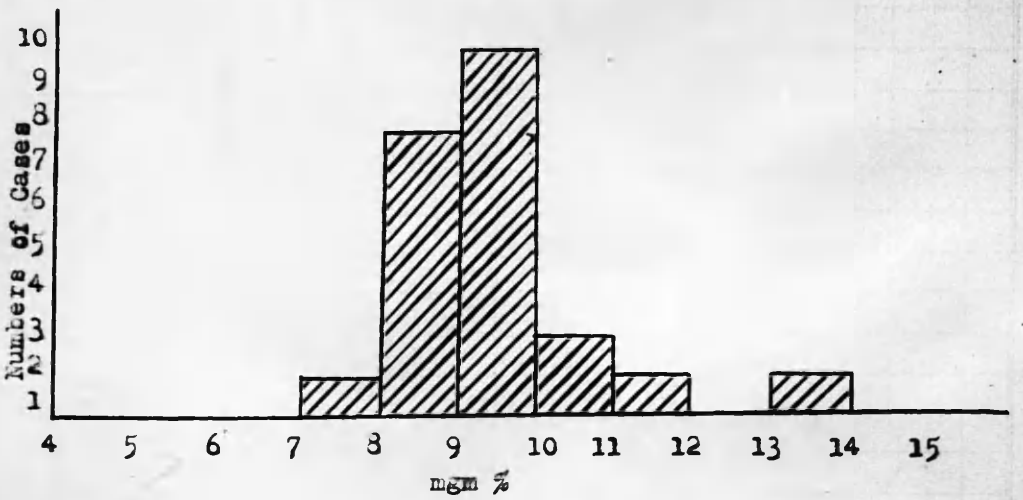
SEASONAL INCIDENCE OF CONVULSIONS NOT ASSOCIATED WITH PRIMARY DISEASE OF THE C.N.S. FOR THE PERIOD 1922 - 26 COMPARED WITH THE ADJUSTED FIGURES FOR 1942 - 46 AND WITH THE AGGREGATE FIGURES FOR TETANY IN ALL PERIODS.



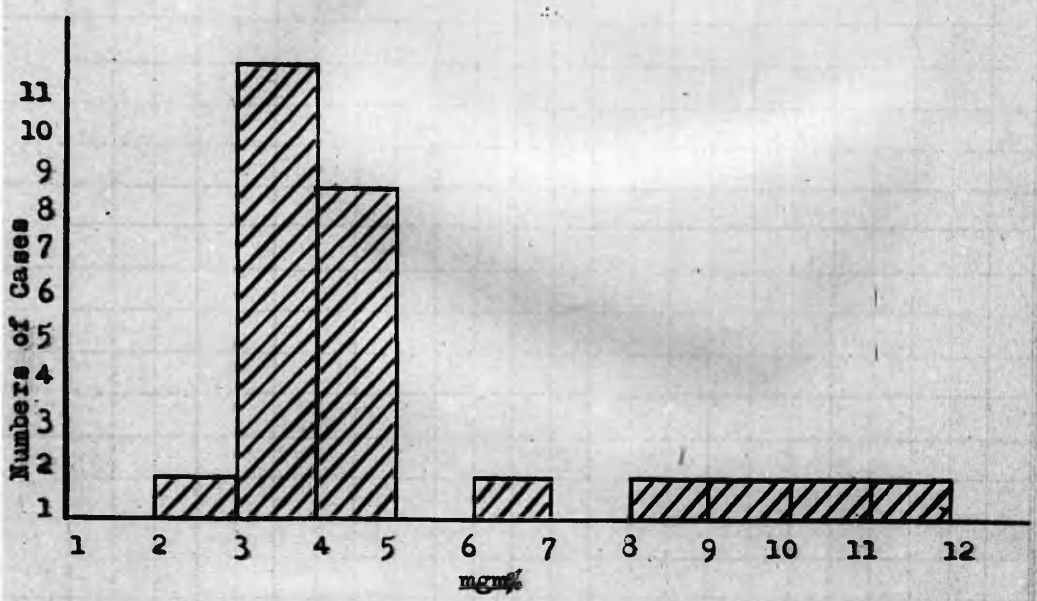
The Serum Calcium in cases of Convulsions not attributable to Primary Disease of The Central Nervous System.



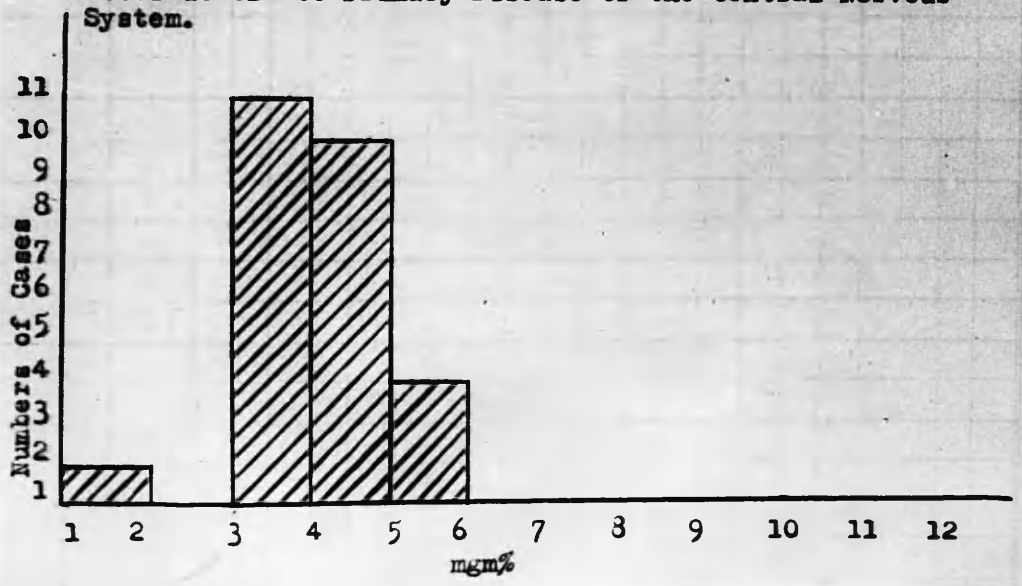
The Serum Calcium in cases of Convulsions attributable to Primary Disease of the Central Nervous System.



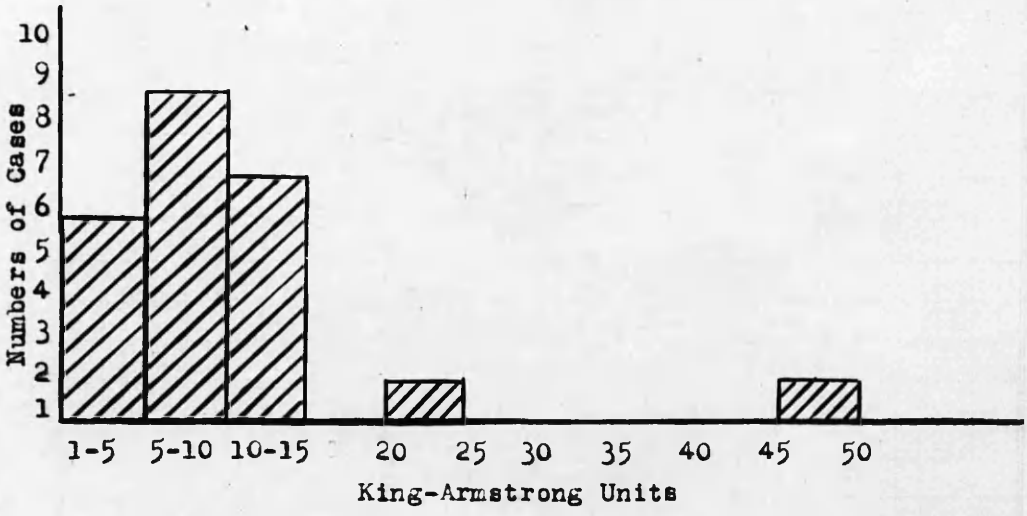
The Plasma Inorganic Phosphorus in cases of Convulsions not attributable to Primary Disease of the Central Nervous System.



The Plasma Inorganic Phosphorus in cases of Convulsions attributable to Primary Disease of the Central Nervous System.



The Plasma Alkaline Phosphatase in cases of Convulsions not attributable to Primary Disease of the Central Nervous System.



The Plasma Alkaline Phosphatase in cases of Convulsions attributable to Primary Disease of the Central Nervous System.