THE PERIODIC SYNDROME*

BY

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The concept of syndrome may be said to be slowly replacing the older and more rigid one of disease entity as the unit of illness in medical thought. This change was well described by Himsworth (1949), and was part of the theme of an address by Sir Henry Cohen (1955).

For most of us the older rules of thought prevailed in our student and resident days; each case had ultimately, if only established in the post-mortem room, a precise diagnosis. A certain faint sense of grievance about this often, I think, persists in some of us—a feeling that there are two sorts of medicine—that of hospital and that of practice.

Used in its proper sense as a “running together” of a number of causative factors and disease manifestations to produce a recognizable clinical picture, the use of syndrome not only, to quote Himsworth, “inspires a far more catholic concept of aetiology and renders pointless many existing controversies,” but also to some extent bridges the gulf between hospital medicine, as we learnt it, and actual practice, in which most of one’s patients are not hospital cases and have no definite labels.

The term periodic syndrome is used by some general practitioners and some paediatricians, but I think it is true to say that it is not widely used or widely recognized. It does seem, however, that it is a valuable one, and that an attempt to define its limitations and implications is justifiable if only because it can well replace a number of other terms which are used only too often, and are either too narrow—as cyclical vomiting; contradictory—as abdominal migraine; or quite incorrect—as “acidosis.” It covers a large group of recurrent disturbances of function which are common in childhood, and which vary from the simple bilious attack to bizarre symptom complexes which may need much unravelling.

Main Features

There are five main features—pallor, headache, abdominal pain, vomiting, and pyrexia—and these or any combination of them may appear in any order to make up the periodic illness, which often seems to recur with a certain rhythmic regularity, though sometimes the intervals are quite irregular. An attack of this sort may last an hour or two, or may, especially when there is pyrexia, continue for several days. Sometimes one symptom may predominate, so that an account of the others may be obtained only by direct questioning, and sometimes a single manifestation may recur for quite a long period before others are added to complete the picture. Less commonly, other symptoms apart from the main five may be added: transient abnormalities of visual sensation, other disturbances of sensation described as giddiness, or alteration in bowel habit with the passage of pale stools for a few days. There are also some cases, lying in the borderland between the periodic syndrome as here described and asthma, in which bronchospasm forms a part of the recurrent attack.

The earliest well-known description of episodes of this sort is that of Samuel Gee (1882). He showed that he saw a certain unity in the diversity of symptoms by beginning his

brief and forthright account of nine cases with the statement, “These cases seem to be all of the same kind.” He used the words “fitful vomiting,” and is often wrongly stated to be the originator of the term cyclical vomiting. Langmead (1905, 1907) gave some detailed accounts of cases regarded as cyclical vomiting. Some of these were fatal and may not have been true examples; one, for instance, at post-mortem examination showed gross fatty changes in the liver and adrenal haemorrhages. He was one of the first to note the presence of ketone bodies in breath and urine, on account of which the idea of “acidosis” was first introduced at that time. There are vivid accounts of the illness in the writings of Still (1909) and Hutchison (1909), and many will recall Hector Cameron’s (1919) charming description of nervous children in his book and in a number of lectures and articles written in the 1920’s. He, too, was interested in the biochemical problem, and also considered the possibility of an underlying alteration in adrenal function as a possible cause—this some twenty years before the birth of “Stress.”

The term periodic syndrome was first used in paediatric literature in a careful and detailed study of 80 cases by Wyllie and Schlesinger (1933). They discussed various possible causative factors, excluding both hypoglycaemia as a direct cause and allergy, and thought that an inherent nervous instability seemed to be the most likely basis. They noted a relationship between migrainous attacks and epilepsy. In 1951 a discussion on periodic illness was held at the Royal Society of Medicine (*Proc. roy. Soc. Med.*, 1951), and a paper on the subject was read by Dr. White Franklin (1952) to the West Hertfordshire and Watford Medical Society. MacKeith and O’Neill (1954) have drawn particular attention to the causative importance of emotional stress in the periodic syndrome. There is very little under this heading in most paediatric textbooks, the symptoms generally being described under cyclical vomiting or psychosomatic problems, but the periodic syndrome has achieved a special chapter in the book edited by Gaisford and Lightwood (1954).

The clinical picture is a diffuse and ill-defined one, so that no case or small group of cases can really be described as giving a typical picture, and it will be better, perhaps, to consider and define (and also limit) the whole group under the usual headings of cause, symptoms, physical signs, diagnosis, incidence, course, prognosis, and treatment.

Cause

The precise mechanism of the recurrent upset is not known. Payne (1951) has suggested progressive biochemical changes—overuse of blood glucose by a nervous hyperactive child leading to a depletion of liver glycogen and excess adrenaline secretion, this in turn leading to gastric stasis and further lowering of glycogen storage, and yet further secretion of adrenaline. He suggests that oversecretion of adrenaline as part of such a biochemical vicious circle could produce all the symptoms. It seems certain that the appearance of acetone bodies is related simply to depletion of liver glycogen (Graham, 1951); the appearance of these products of incomplete fat metabolism is incidental and is readily compensated by the mechanisms controlling blood pH, and acidosis does not occur. The “white” stools noted by earlier writers still occur, though not noticed so often, and this might suggest a temporary liver dysfunction.

That these episodes are epileptic variants or masked epilepsy has been suggested by Millichap (1955) and Wallis (1955). Epilepsy itself is, however, far from clearly defined. Gowers (1892) regarded it as including the slightest disturbances on the surface of the stream of consciousness, and if we accept this most of us have at some time or other, and especially in childhood, had a few fits—transient dreamy states or recurrent sensations of indescribable taste or smell or *déjà vu*—though we would not be prepared to admit this when applying for renewal of our driving licences. Most of us know what we mean when using the word epilepsy—the abnormal movements and the losses of consciousness which, however brief, are always precipitate—and also accept

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psychomotor and purely motor variants. The matter here is one of definition and limitation, perhaps arbitrary, but without which the unifying concept in medicine can only too quickly extend to the point of losing coherent meaning.

While the exact mechanism of the attacks is not yet understood, there are clearly a number of causative factors.

1. *Inherent and familial tendency to periodic functional upset.*—A history of similar attacks in another member of the family is strikingly frequent, and commonly one or other parent can remember similar attacks in childhood. There is often a family history of travel sickness and, of course, migraine. This impression of familial trend is such a strong one that we can surely accept it, at least until it has been statistically disproved by comparison with the families of non-affected children.

2. *Some focus of infection in upper respiratory tract, recurrent exacerbations of which seem to have a trigger effect.*—Most frequently this is a tonsillitis, the direct symptoms and signs of which may often be so slight as to escape notice.

3. *Nervous element.*—Ryle (1948) coined the valuable phrase "visceral neuroses"—bad habits involving the vegetative system but with the same tendency to become established as those occurring on the level of conscious behaviour, and in which a concentration of attention through anxiety, and especially resulting from excessive treatment, tends to make the symptoms worse. He had in mind conditions such as asthma, spastic colon, and spasmodic dysmenorrhoea, but visceral neuroses might also include the periodic syndrome in childhood, in which anxiety in either parent or child directed to the symptoms, and much treatment, can often be observed to make the symptoms more troublesome and persistent. The relationship of an individual attack to some emotional strain can sometimes be clearly seen, and the rise in tension setting off the train of symptoms may derive from serious underlying disharmony; but the cause may be a slight one, and may even consist simply in dislike of some proper activity such as going to school or eating rice pudding.

These three are the main causative factors; less commonly, other minor factors may play a part—tiredness, a hot and stuffy room, a bright flickering light, or an indigestible meal. Several of these factors may operate together or in complementary fashion: in a child debilitated by recurrent infection very small emotional causes may be enough to set off the train of symptoms, while in a tense and emotionally disturbed child a minimal tonsillitis may be the trigger. Where there is a familial tendency to periodic upset the first manifestations may well appear with the increased infections, rapid growth, and increased fatigability of early school life.

Symptoms and Physical Signs

The symptoms have been described in outline and are now considered in more detail.

Pallor is often the first symptom, and may be described in answer to the question, "Do you know when an attack is coming?" Parents may also notice dark shadows under the eyes or say "the eyes look dark." At the same time the child is unusually quiet or, less commonly, becomes difficult and restless. Pallor may go on to fainting—the church faint which every schoolmaster knows.

Headache may be frontal or unilateral. Sometimes, and especially when there are also visual disturbances, the child may be frightened or upset without being able to describe his symptoms. Headache becomes a commoner symptom in older children as vomiting and abdominal pain decrease in importance, and there is sometimes a gradual merging of symptoms into the adult migraine or recurrent sick headache. Visual symptoms indescribable at the time may be described in later life in retrospect.

Vomiting is commonly repeated and may lead to severe collapse. The case in which vomiting is the main symptom is of course the one which tends to be called cyclical vomit-

ing. On the other hand, the symptom may, as Gee (1882) noted, be absent or quite overshadowed by pain. Sometimes there is much nausea but no vomiting.

Abdominal Pain.—This is the most difficult symptom to evaluate. Abdominal pain in children, especially small ones, tends to be a universal symptom resulting from every sort of physical and emotional cause. The pain is usually central, and the account may be that of an aching discomfort or of colic, and it may be severe. Sometimes noisy borborygmi precede or accompany the pain.

Pyrexia.—This is perhaps the least frequent symptom, but may cause most anxiety, and when recurrent febrile episodes occur with at first no other manifestation much investigation is apt to be carried out, and may indeed be very necessary. No characteristic pattern of temperature occurs, but fever may come and disappear remarkably quickly. This is, to quote Gee again, the "febris ephemera" which the ancients distinguished as insignificant in comparison with remittent, continuous, and other fevers.

Physical Signs.—By definition the periodic syndrome presents no organic signs of structural disease. One often recognizes a type of child—alert, intelligent, and quick to respond, well up in class in spite of having missed much school, and often seeming to get more out of life in spite of his symptoms than his more stable brother. During an episode the appearance of pallor and collapse may be such as to cause great alarm, especially when symptoms first occur. Temperature and pulse may be raised, the breath may be offensive or have an odour of acetone. Apart from pallor, other vasomotor phenomena are common, especially patches of flushing.

Diagnosis

Diagnosis is an intellectual process depending acutely on personal judgment and knowledge of the individual and his background, and not on ancillary investigations, which are needed only to exclude structural disease; thus the periodic syndrome is specially the diagnostic field of the family doctor.

Differentiation from many more serious conditions is often both important and difficult. Fever may be due to an infective process; or a minimal infective process may be present with fever and other symptoms quite out of proportion. Episodes of headache and vomiting may precede other signs of increasing intracranial pressure. Abdominal pain may have many causes, from the rare one of tuberculous mesenteric adenitis to the common one of acute appendicitis; though it is true, as White Franklin (1952) noted, that in appendicitis pain is not usually recurrent over a long period. Indications of the occurrence of tuberculous mesenteric adenitis may show in the form of areas of calcification, without necessarily proving a relationship to the symptoms. Non-tuberculous mesenteric adenitis probably occurs in children commonly as a response to infection in either the respiratory or the alimentary tract, and the relationship of the enlarged glands often seen at laparotomy to recurrent pain is a most uncertain one. Acute non-specific mesenteric adenitis as described by Aird (1945) probably represents simply one small aspect of the periodic syndrome which is often noticed by the surgeon. Ileitis, ileo-colitis, or recurrent attacks of small-gut obstruction due to a band or abnormal mesenteric attachment are less common possible causes. Abdominal pain may be a presenting symptom in rheumatic fever or in the Schönlein-Henoch syndrome. Chronic or recurring intussusception is a rare cause of pain occurring in episodes. In elucidating cases in which pain is prominent, inspection of stools, examination of urine, and a tuberculin test will be needed always, and an x-ray examination of the alimentary tract occasionally.

Differentiation from epilepsy may be difficult or impossible, and there will always be some cases lying in the borderland of epilepsy, classically described by Gowers (1907), in which judgment may have to be suspended for a time. E.E.G. tracings may help a little and may in future help more—particularly, perhaps, in the obscure disturbances of

consciousness becoming known as temporal lobe epilepsy. Response to anticonvulsant drugs, especially phenobarbitone, may be of some slight diagnostic significance, but a diagnosis of epilepsy should never be based on this alone.

True syncopal attacks as described by Sheldon (1952) are uncommon and should probably be considered separately, and fainting with no other symptom or with sweating may in rare cases be directly related to hypoglycaemia. The term "vaso-vagal" really has no meaning and is best abandoned.

Incidence, Course, and Prognosis

It is impossible to say how common periodic upsets of this sort are. Few of us, particularly in childhood, have escaped occasional bilious attacks and sick headaches, and complete vegetative stability must be rare. Of new patients seen in the paediatric out-patient clinic, at least one in ten is, in my experience, a case of this type, but many go to other departments. Some in whom headache is prominent reach the eye department. Many in whom there is fever in each episode, and whose tonsils are suspected, go to the E.N.T. surgeons. Where abdominal pain is prominent many children are first referred to the surgeon. A few are referred directly to the psychiatrist or the child guidance clinic.

This illness is best seen against a background of individual and family lifetimes. Generally it can be said that the periodic syndrome is most troublesome during the period of rapid growth and first massive exposure to infection—the early years of school life—becoming less troublesome in the later sturdier years, with perhaps some recurrence of more upsets at puberty. There is also a tendency for fever to be more prominent in younger children, and headache to appear as this and abdominal symptoms diminish in later childhood and adolescence. Migrainous headaches, in turn, often disappear towards middle age. Throughout the affected lifetime symptoms are accentuated in periods of debility or emotional stress.

Death from cyclical vomiting has been recorded in a few cases (Brown, 1954), but must be extremely rare, though intense and continued vomiting may lead to a state of grave collapse. Professor Graham noted that no fatal case had occurred in the records of the Royal Hospital for Sick Children, Glasgow. Thus the prognosis for survival is excellent. Mostly, symptoms cease in late childhood or adolescence.

Treatment

Treatment can be described under two headings—the acute attack and the general management. Aspirin is without doubt the most effective drug. Given early it may abort an attack, and given in adequate and repeated doses it almost always cuts it short. Diet during acute symptoms should be limited to fluids sweetened with sugar or glucose, and these should be given in as large amounts as the child will take. Prolonged, repeated, and severe vomiting may be an indication for intravenous fluid and glucose, but occasions for this are rare. In my experience, on the last two occasions when they were given, recovery had begun before the transfusion was set up, and, once started, was so rapid that it is doubtful whether this measure was really necessary. Phenobarbitone, given either at the onset of an attack or in regular dosage over a period, may help.

General Management

General management of these cases is difficult and at the same time most rewarding. It involves a watch, a periodic overhaul, an absence of fuss, and the establishment of a special degree of understanding between doctor and parents. Trigger causes, whether infective, emotional, or environmental, must be sought, explained, and where possible removed. Simple measures to improve general health may be indicated, and it is very important that diet should not be restricted between attacks; many children are still quite unnecessarily deprived of butter and cream and cod-liver oil on account of these symptoms. The parents must be

made to understand that, while the periodic illness is of no serious consequence in itself, these children are at special risk in that the early symptoms of more serious illness may well be regarded as just one of the usual episodes: the child is in the position of the little boy who repeatedly cried "fire." At the same time it is of great importance that too much is not made of the attacks, and that they are not allowed to interfere more than is necessary with any usual activity.

The establishment of this sort of understanding in all honesty, without any dissembling or use of magic, calls for all that is best in the modern general practice of medicine. Indeed, I think it is true to say that there is no other branch of medicine in which it is possible.

The question of surgical procedures will commonly arise. Tonsillitis is a common trigger cause, and removal of tonsils which are the seat of recurrent infection may make the attacks less frequent; but the tonsils should not be removed unless there is definite evidence that they are damaged by recurrent inflammation. Often when abdominal pain is a prominent or main symptom, laparotomy and appendicectomy will be carried out. Appendicitis is a common and dangerous illness in childhood, and one in which diagnosis can be exceedingly difficult, and when there is some doubt whether the symptoms may or may not be due to an inflamed or obstructed appendix it is probably always better to operate than to delay. Also, it is very striking how often the removal of a perfectly normal appendix is followed by the permanent cessation of symptoms. Nervous and emotional causative factors are almost always prominent in the periodic syndrome, if not quite so important as MacKeith and O'Neill (1954) would have us believe, and psychotherapy in this illness is most speedily effective when carried out by the surgeon. Something quite definite has at last been done by someone who knows his own mind and knows just what to do.

Neither of these considerations should, of course, lead us to indiscriminate appendicectomies, and this is one of the problems in which in order to reach a decision we often work better as a team than as individuals. Of this team the family doctor is, or should be, the most important member, as he is in the management of the syndrome as a whole.

Conclusion

Finally, I think I should end on a note of warning: periodic syndrome is a provisional diagnostic term which, I have tried to show, has both intellectual and practical merits. It is of great importance that it should never be accepted as an irrevocably final diagnosis, that it should not become the Periodic Syndrome. If we remember this we shall be in no greater danger of missing cases of appendicitis or cerebral tumour or tuberculous meningitis, and we shall have a useful label of identity to attach to a common and troublesome illness which has suffered in the past, and continues to suffer, from many misnomers and much confusion of thought.

Summary

An attempt has been made to define, describe, and limit the periodic syndrome, this term being used to cover many of the common recurrent upsets of childhood.

The definition includes bilious and migrainous attacks, and periodic syndrome can replace the unsatisfactory terms cyclical vomiting, abdominal migraine, and "acidosis."

The exact mechanism of episodes of this sort is not understood. A number of predisposing and precipitating causative factors are discussed.

Simple symptomatic treatment with aspirin and sweetened fluids is often effective.

The diagnosis and management of these cases, involving continued observation and personal knowledge and

understanding of child and family, is especially the field of the family doctor.

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MULTIPLE MYELOMATOSIS SIMULATING HYPERPARATHYROIDISM

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It is known that hypercalcaemia may occur in multiple myelomatosis (Caylor and Nickel, 1933; Bodansky and Jaffe, 1934; Gutman *et al.*, 1936), and that this is sometimes accompanied by hypercalcuria (Caylor and Nickel, 1933; Nassim and Crawford, 1950). These findings have, on occasion, given rise to difficulty in the differential diagnosis between multiple myelomatosis and hyperparathyroidism. In almost all cases of multiple myelomatosis the serum phosphorus is normal or elevated, but, since this may also occur in cases of hyperparathyroidism in which renal impairment has developed, the serum phosphorus level may not be of help in the differentiation between the two conditions. In hyperparathyroidism there is thought to be a diminished reabsorption of phosphate by the renal tubules (Albright and Reifenstein, 1948), and this is regarded as a diagnostic test for parathyroid function.

This paper reports a case of multiple myelomatosis in which, in addition to hypercalcaemia and hypercalcuria, there was a diminished reabsorption of phosphate.

Case Report

A woman aged 46 had had, for about six years, abnormal thirst with associated polyuria. Apart from tiredness for a year, her health was good until New Year's Eve, 1954. When dressing she felt a sudden sharp pain in the sternum, with a sensation of something giving. The following evening she felt sick and vomited, and from that date until her admission to hospital three weeks later she vomited three or four times daily. Her medical history and family history were negative.

On admission she was pale and moderately dehydrated; there was a protuberance about the middle of the sternum; the blood pressure was 170/100. No other abnormalities were noted. X-ray examination revealed a double fracture of the upper end of the sternum. There was a moderate degree of demineralization of the vertebral column and ribs. Films of the hands, arms, legs, pelvis, and skull did not show any definite changes. There were no renal calculi, nephrocalcinosis, or calcification of soft tissue. The x-ray appearances were thought to be consistent with the diagnosis of hyperparathyroidism.

Biochemical Data

Date	Serum Calcium (mg./100 ml.)	Serum Phosphorus (mg./100 ml.)	Urea (mg./100 ml.)	Carbon Dioxide Combining Power (ml./100 ml.)	Alkaline Phosphatase (K.A. Units)
1/2/55	16.2	—	48	—	—
4/2/55	19.1	5.9	108	70	9
7/2/55	12.9	3.2	72	62	—
9/2/55	15.7	3.5	60	—	—
15/2/55	15.2	3.3	67	65	11

The biochemical findings are shown in the Table. The original value for phosphorus was discounted because it had been determined on heparinized blood, which is unsuitable for the determination of phosphorus (McGeown *et al.*, 1955).

The glomerular filtration rate, as estimated by a continuous intravenous infusion of inulin (mean of three periods) was 18.9 ml. a minute. The urinary clearance of phosphate, expressed as a percentage of the inulin clearance, was 73% when the serum phosphorus level was 3.2 mg. per 100 ml. This represents a greatly increased tubular rejection of phosphate. The specific gravity ranged from 1008 to 1020. There was a moderate degree of albuminuria, but Bence Jones protein was not present. The patient was given a low-calcium diet (154 mg. in 24 hours) for 12 days, and during this period the daily urinary excretion of calcium varied

FIG. 1.—Biochemical data.