CLINICAL REVIEW

Haemocytic periodicity and periodic disorders: Periodic neutropenia, thrombocytopenia, lymphocytosis and anaemia

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Summary

Evidence has accumulated of rhythmic numerical oscillation of each of the blood cells either independently or in combinations.

The cyclic changes originate in the marrow of some normal persons and animals without causing illness, and can be induced experimentally.

In more than 100 reported instances, periodic oscillations of various cells were accompanied by respective episodes of the disorders named in the title. The disorders may be transitory but usually recur throughout life and occasionally are fatal. All resist therapy. Features in common suggest an interrelationship of the haemal disorders and other disparate heritable periodic diseases.

Theoretically, the rhythms are regulated by ubiquitous, inherent, intracellular bioclocks controlled hypothalamically or neurohumorally in relation to a feedback mechanism. Reactions to long cycles are of greater clinical importance than disturbances arising from the circadian rhythm.

Introduction

After the establishment of periodic (cyclic) neutropenia as an entity in 1949 (Reimann & De Berardinis, 1949) nearly fifty cases were added to the forty-two cited in 1963 (Reimann, 1963). Because the trouble originates in the marrow, the term periodic myelodysplasia was proposed. The broad term applies if the numbers of more than one kind of haemocyte oscillate synchronously or independently as they often do. When neutrophils, platelets, monocytes, lymphocytes and erythrocytes alone oscillate, specific designation is appropriate. By including periodic disorders related to the numeric fluctuation of various haemocytes, the total number of reported cases involving the blood exceeds 100. Many unrecognized ones, no doubt, exist.

Periodic haemocytic changes are either primary or are associated with menses, lymphomas and immunosuppressive therapy. In both circumstances, the

involvement is either overt or clinically inapparent except for the numeric cellular oscillation. Periodicity escapes detection unless cells are counted at short intervals in patients, in healthy genetic relatives or others. Serial counts have disclosed periodicity in some patients regarded as cases of continuous, congenital or hereditary neutropenia (Morley, Carew & Baikie, 1967).

Periodic neutropenia is heritable. Probably thrombocytopenia, lymphocytopenia and anaemia also are genetically transmissible. The disorders are not always benign. Concurrent infection or bleeding occasionally is fatal. Therapy generally is ineffectual; the symptoms alone are meliorated, cellular cycles usually persist. This review stresses the periodicity of various haemocytes, their interrelated disorders and frequent heritability as described in published cases and personally observed ones. Articles cited in references recount detailed clinical features.

Periodic neutropenia

Heredit

Morley's studies, particularly his opportunity to study five afflicted families, provided much information. Twenty members had had overt disease, usually since infancy. Neutrophils also fluctuated rhythmically in several symptomless members. Some of them had continuous neutropenia with cycles of further depression. The tempo ranged from 15 to 35 days, averaging 20. Synchronous monocytosis and fever occurred often. Anaemia, eosinophilia and thrombocytopenia concurred episodically in three relatives. An autosomal dominant trait of high penetrance and variable manifestations characterized the afflicted families (Morley *et al.*, 1967).

Table 1 portrays thirty-seven primary cases accruing after forty-two previously recorded ones and includes a few I omitted in 1963. Table 2 shows ten cases regarded as secondary neutropenia, making a total of eighty-nine in all. Of the seventy-nine primary ones, forty-two were in females, thirty-seven

TABLE 1. Periodic neutropenia

Author	Sex	Age (years)	Age at onset (years)	Periodicity (days)	Monocytosis	Lymphocytosis	Thrombocytopenia	Eosinophilia	Familial	Unusual features
Lorre & Denys (1960)	F	8	3/12	23	+	+		+		Rapid ESR
Toro <i>et al.</i> (1960)	M	2	4/12	19 (21 days after cortisone)	+		Thrombocytosis			Sialorrhoea, diarrhoea, seizures
Bray (1960)	F	9	?	21						Serious infections, steroids ineffective
Gorlin & Chaudry (1960)	F	8	4	21					+	
Malooly (by letter)	M	54	33	28	Mono-cytopenia					Prednisone meliorated symptoms only
Alestig (1961)	F	58	54	14						Prednisone meliorated symptoms only. Spontaneous remission 1 year
Telsey <i>et al.</i> (1962)	F	14	4/12	±21						fever 40° C
Videbaek (1962)	M	29	2	21	+				+	Splenectomy and steroids ineffective
	M	2	10/12	21						Fever 39 °C
	M	18	1	21; later 14						Fever 38 °C
Wade & Stafford (1963)	M	38	32	21–28						Splenectomy, prednisone relieved symptoms only
Coutel, Morel & Thomet (1963)	M	6	1	±21	+					Pulm. abscess
Smith (1964)	M	20	6	14–20						Hypergamma-globulinaemia
<i>Journal of the American Medical Association</i> (1965)	F	22	16	?						Five episodes of pancreatitis
Simonsen (1966)	F	21	17	±21		Lymphocytopenia				Abdominalgia, arthralgia
Morley (1967) Twenty cases	7M 13F		Usually childhood	15–35	Often				7 familial	Periodic arthralgia in three
Felitti (by letter)	F	6	?	?						Died, peritonitis
Waldron-Shah (by letter)	F	35	8	21	+	+		+	Doubtful in several relatives	Stethalgia, abdominalalgia, arthralgia, erythema, xerostomia, diaphoresis, diarrhoea, oedema, somnolence, pallor

in males. They began in infancy in twenty-seven and after age 60 in three. Periodicity generally ranged from 14 to 28 days, mostly 20 or 21. Monocytosis or monocytopenia, lymphocytosis or lymphocytopenia, eosinophilia and thrombocytopenia or thrombocytosis characterized some instances. The recorded numbers depended upon whether cells were counted during episodes or in the intervals. Published reports do not always specify the timing. Serious infections occasionally ensued and seven ended fatally. Familial involvement was evident in eleven instances. In several groups, symptomless relatives

were neutropenic or had recurrent oral ulcers without detected rhythm. Pregnancy suppressed, worsened or had no effect on episodes. Corticosteroids meliorated the symptoms in a few, but had slight or no effect on the cellular cycles. Splenectomy seldom was justified. As found in common with other disparate periodic disorders, synchronous fever, sialorrhoea, xerostomia, exanthems, arthrosis, abdominalalgia and diarrhoea occasionally occurred.

Similar to human disease, six grey Collie dogs had heritable periodic neutropenia. Three had concurrent gingival and dermal ulcers, arthralgia and

fever. Neutropenic episodes recurred every 8–13 days averaging 10 with compensatory monocytosis (Lund, Padgett & Ott, 1967).

Complement anomaly in periodic neutropenia

Study of my patient E.C. disclosed the inhibitor of C1 esterase reduced from a normal 5.6 units to 3.6 u and 4 u in two respective episodes, and to 4 u in an interval. His whole serum complement activity during the two episodes measured 34 u and 58 u, and in the symptomless interval 44 u (normal 62 ± 19 u) (Reimann, Coppola & Villegas, 1970). Splenectomy failed to help the patient. Testosterone meliorated the symptoms for a time by preventing extreme neutropenia. It induced concurrent monocytosis, and lymphocytosis and increased the granulocytic reserve as demonstrated by the pyrogen stimulation test (Brodsky, Reimann & Dennis, 1965).

Aysmptomatic and secondary periodic neutropenia

Morley demonstrated symptomless neutropenia at intervals of 14–23 days in eight of eleven normal men from unaffected families. Similar oscillation accompanied menses in two normal women (Morley, 1966). The behavior indicates the existence of an underlying inherent biorhythm and a feedback mechanism affecting the formation of cells. This action in genetically susceptible persons provokes disease (Reimann, 1948). In one of my patients with periodic polyserositis (Case 1, Reimann, 1948), periods of symptomless neutropenia, monocytosis and lymphocytosis occasionally recurred separately from episodes of her disease.

After the deliberate impairment of immunity, Alexander demonstrated fluctuation of antibacterial activity of neutrophils in cycles usually of 14–24 days in patients and monthly in dogs. The activity was independent of the number of neutrophils. Injury and immunosuppressive therapy adversely affected phagocytosis but did not abolish the basic cycle. As in periodic neutropenia, infection occasion-

ally concurred (Alexander, Dionigi & Meakins, 1971). Morley & Stohlman using cyclophosphamide reduced the number of neutrophils in dogs and lowered neutropenia every 11–17 days (Morley & Stohlman, 1970). A hypothetic feedback control was discussed in detail (Morley, 1970).

Patients with polycythemia or leukaemia and secondary periodic neutropenia listed in Table 2 all were adults. The rhythm of neutropenia ranged from 30 to 120 days. Its amplitude probably was extended to that length by the gravity of the underlying diseases or by therapy thereof. Thrombocytopenia concurred in four. Episodes of neutropenia affected agammaglobulinemic children (Telsey, *et al.*, 1962).

Neutropenia and pancreatic disturbance

Neutropenia and pancreatic dysfunction affected a child at 21-day intervals (Colebatch *et al.*, 1965). In six other patients, a 'new' entity, in one instance familial, consisted of pancreatic insufficiency, anaemia, neutropenia and occasional thrombocytopenia and purpura. The tabulated data suggest unnoticed recurrent episodes of neutropenia (Shwachman *et al.*, 1964). Bodian also commented on the combination of congenital pancreatic hypoplasia, neutropenia and thrombocytopenia (Bodian, Sheldon & Lightwood, 1964). Fluctuation of the three factors appears in the tables of two of my patients, but cell counts were too widely spaced to detect regular periodicity. Elsewhere I described periodic pancreatosis without attention to neutrophilic changes (Reimann, 1962).

Periodicity during haemal diseases

In a polycythemic patient, the number of neutrophils fluctuated every 15 days, the platelets every 27 days, both within the normal range. A reticulocyte cycle of another patient lasted 17 days (Morley, 1969a). As noted by Morley and others, periodic neutropenia occasionally accompanies lymphomatosis (Morley, Baikie & Galton, 1967) (Table 2). In

TABLE 2. Secondary periodic neutropenia

	Disease	Sex	Age (years)	Age at onset	Periodicity (days)	Mono-cytosis	Thrombo-cyto-penia	
Morley (1969a)	Polycythemia	M	68	8	15	+	+	Another patient had periodic reticulocytopenia at 27-day cycles
Morley, Baikie & Galton (1967)	Myelogenous leukaemia	F	42	?	50–55		+	Modified by therapy
	Leukaemia	M	45	?	30–35		+	Modified by therapy
	Leukaemia	F	60	57?	30			Modified by therapy
	Leukaemia	M	37	35?	100–120			Modified by therapy
Kennedy (1970)	5 patients Myelogenous leukaemia				30–50		+	

Postgrad Med J: first published as 10.1136/pgmj.47.549.504 on 1 July 1971. Downloaded from http://pmj.bmj.com/ on April 26, 2023 by guest. Protected by copyright.

Kennedy's five patients with myelogenous leukaemia treated with hydroxyurea, leucocytes and platelets fluctuated in 30–50-day cycles (Kennedy, 1970). Rhythm may be obscured by therapy or by the gravity of the primary disease. On the other hand, either therapy or the disease induces oscillation.

Secondary lymphocytosis

Lymphocytosis occasionally accompanies normal menses (Minot, 1936). During lymphocytic leukaemia in a patient, spells of fever, polyuria and facial oedema appeared at 5–10 day intervals. Four months of observation disclosed a lymphocyte-lymphoblast number of about 280,000 which diminished to normal during episodes. The 2% of segmented cells diminished slightly in unison. An attack of herpes zoster temporarily lengthened the rhythm to 15 and 17 days. On one occasion, withdrawal of spinal fluid promptly increased the number of lymphocytes and averted an expected febrile episode. The event suggested central neural or neuro-humoral regulation (Stacher & Bohnel, 1958). The idea was based on the experimental demonstration of prompt leucocytosis after mechanical disturbance of the hypothalamic area. Although governed centrally, the effect presumably is mediated humorally on the marrow (Rosenow, 1951).

Periodic thrombocytopenia

Since Demmer's report, at least six primary cases have been described (Demmer, 1920). In one instance, a man had episodes of bleeding for 42 years. His platelets diminished monthly to fewer than 50,000/mm³ after reduction of megakaryocytes in the marrow. The numbers of leucocytes and erythrocytes remained normal. Prednisone was ineffective (Engstrom, Lundquist & Soderstrom, 1966). A man, aged 37, had five episodes of thrombocytopenia and

bleeding, each one worse until death from cerebral haemorrhage. Episodes came at predicted 21-day intervals. Platelet counts ranged from 0 to 500,000/mm³. Splenectomy and prednisone had failed to help (Wasastjerna, 1967).

Table 3 lists the six patients. The disorder began in middle age. Periodicity ranged from 21 to 39 days. One patient had haemolytic anaemia. One died during an episode. Splenectomy and corticosteroid therapy had no effect.

Asymptomatic and secondary periodic thrombocytopenia

Morley discovered a 21–35-day rhythmic oscillation in the number of platelets in normal persons. In occasional susceptible persons like these, bleeding may occur regardless of the degree of thrombocytopenia (Morley, 1969b). Rhythm may be overlooked unless serial counts are made. If these are made on patients with essential thrombocytopenic purpura, rhythmic fluctuation of platelets may become evident in some of them. Correct diagnosis obviates splenectomy which is ineffective for periodic thrombocytopenia.

Thrombocytopenia and purpura also occur in rhythm with menses (Pohle, 1939). In a woman aged 46, episodes of epistaxis, menorrhagia and purpura recurred every 28 days for 8 years. Episodes usually coincided with menses and also happened in the mid-period. Platelets varied in number from 10,000 to 300,000. The marrow contained nonfunctioning megakaryocytes fluctuating in rhythm. Normal hormonal amounts remained constant. Because episodes recurred regularly after oophorectomy (Skoog, Lawrence & Adams, 1957), prior relation to menses may have been coincidental. In another woman, thrombocytopenic purpura happened at every other menstrual flow (Pepper, Liebowitz &

TABLE 3. Periodic thrombocytopenia

	Sex	Age (years)	Age at onset	Periodicity (days)	Symptoms	Comment
Demmer (1920)	M	61	55	28	Purpura	Irregular synchronous lymphocytosis. Death from nephritis
Skoog <i>et al.</i> (1957)	F	46	38	28	Epistaxis, menorrhagia, purpura, mucosal lesions	With and between menses. Persisted after oophorectomy
Dameshek (by letter)	F	42		27	Episodes of haemolytic anaemia, thrombocytopenic purpura	Had prior splenectomy for haemolytic anaemia
Wasastjerna (1967)	M	37	33	21	Severe bleeding	Died in predicted episode from cerebral haemorrhage. Splenectomy and steroids no help
Engstrom <i>et al.</i> (1966)	M	61	59	39	Purpura	'Absolutely regular sequence'
Bernard & Caen	M	54	17	Monthly	Buccal ulcers, subcutaneous haemorrhages	Corticosteroid and splenectomy, no effect
Candura (1960)						
Fourteen cases related to menses						

Lindsay, 1956). In the published case record, lower platelet counts appear without comment at about 20-day intervals suggesting a *circa* 21-day periodicity. Candura described two cases related to menses and cited reports of at least twelve others chiefly in Italian and German journals (Candura, 1960). These are regarded here as secondary but if included in Table 3 would make a total number exceeding twenty. More cases, no doubt, will be diagnosed when serial counts are made.

Regardless of known platelet participation, bleeding and purpura can be induced periodically in religious stigmatists presumably by wilful excitement of the autonomic neurovascular system (Agle & Ratnoff, 1962).

Periodic erythrocytic oscillation

A 7-year-old boy had 'congenital hypoplastic anaemia and periodic erythrocytopenia' since infancy. At first, episodes came at 2–3-month intervals, later about twice yearly. The marrow during episodes showed erythrocytic aplasia. The child was well between episodes and developed normally otherwise. An infant brother died from anaemia (Gordon & Varadi, 1962).

A man who died at age 21 from Hodgkin's disease had had numerous episodes of anaemia with increased sedimentation-rate, lymphocytopenia and fever. Two-week-long episodes alternated with about 3 weeks of relative good health. Five episodes were observed during 5 months in a hospital. Because of brisk erythropoiesis in the marrow, his physicians regarded the periodic anaemia as of haemolytic origin (Ranløv & Videbaeck, 1963).

Ashby observed 8–16-day cycles of haematopoiesis in animals and changes in human erythrocyte numbers every 14 days (Ashby, 1948). In Morley's polycythemic patient, independent reticulocyte, neutrophil and platelet cycles indicated that normal homeostatic controls still were functional (Morley 1969a). A 14-day oscillatory rhythm of reticulocytes appeared in dogs. Bleeding and transfusion shifted the oscillatory phases (Morley & Stohman, 1969).

Discussion

In the past 20 years, clinical interest in life-long recurrent disorders in otherwise healthy persons has increased. Many examples have been delineated and added to those described previously. They are included in a proposed group of disparate nosologically related entities. Common to all are heritability, precise or irregular periodicity, overlapping features, menstrual suppression of episodes, resistance to therapy and similar serum-complemental defects (Reimann, 1963).

Considering the interrelation of periodic disorders, the case described to me as one of possible

periodic neutropenia by Waldron-Shah (Table 1) is pertinent. The patient has constant leucopenia with periods of neutropenia every 21 days 'predictable to the day'. Other leucocytes increase reciprocally. During episodes, the usual oral ulcers appear. But in addition, there occur fever, severe abdominalgia and stethalgia, arthralgia of elbows and knees, and oedema of the eyelids, face, palate and hands. These features respectively characterize periodic polyserositis, periodic arthrosis and periodic oedema. Myalgia, sialorrhoea, xerostomia, erythema, somnolence, blurred vision, diaphoresis, tachypnea, vomiting and diarrhoea common to all periodic disorders also concur at times in the episodes as autonomic reactions. An electroencephalogram was normal. Because none of the symptoms predominate consistently, a basic diagnosis of periodic neutropenia with composite symptoms is appropriate.

It may be recalled that a patient with periodic polyserositis (Case 1, Reimann, 1948), cited above had occasional separate periods of neutropenia. As indicated in Table 1, Simonsen's neutropenic patient had abdominalgia and arthralgia. Some family members of Morley's group had arthralgia, and Lorre's patient had synchronous sialorrhoea, diarrhoea and seizures. Periodic neutropenia with pancreatic disturbance was mentioned above. Systemic disturbance is obvious.

Regarding periodic haemal disorders, several entities have emerged. According to the tables, primary periodic haemal disorders begin at any time of life, occasionally are familial, have overlapping features, resist therapy and occasionally are fatal. Evidence of similar periodicity emerges during unrelated diseases. Periodicity can also be induced experimentally in man and animals. Various haemal cells oscillate in number independently or in combinations. When independent, specific names may be applied; for combinations, the term myelodysplasia seems apropos. Synchronous increases in numbers of certain cells may be compensatory or specific.

The immediate site of disturbance is in the marrow. Why the oscillatory rhythm varies in days, weeks or months, often precisely, in different patients and for different cells is unknown. Occasional temporal association with menses may indicate either hormonal incitement or the synchronous effects of two separate biorhythms. Morley's discovery of similar haemocytic cycles in asymptomatic members of afflicted families, in normal persons, and in animals indicates the ubiquity of the rhythm. Exaggeration of oscillation or oscillation in susceptible persons evokes periodic disease.

Alexander demonstrated depressed antibacterial action of neutrophils in the usual 14–24-day rhythm in normal persons. At the nadir of action, infection occurred in one person. Infections also occurred at

the time in burned patients and in others treated with immunosuppressive drugs. The behavior may be one variable factor favoring unexpected recurrent infections. Long biorhythms as principles of life and reactions to them are of much more clinical importance than disturbances incident to the circadian rhythm.

Concerning the ultimate cause, no demonstrable inborn-error of metabolism or endocrinal influence participates. The circadian rhythm, extraneous geophysical or cosmic influences have no bearing. Whether a complement disturbance observed in the single case of periodic neutropenia is a characteristic and relevant to the cause cannot be said without further evidence.

Theoretically, an inherent biorhythm excites the hypothalamic area, the effects of which are mediated neurally. Pertinent to the blood, Richter postulated the existence of local bioclocks or Zeitgebers in cells of the marrow (Richter, 1960). An action-phase in the stem cells of each of the haematopoietic components may synchronize independently to cause neutropenia, lymphocytopenia, thrombocytopenia, reticulocytopenia or anaemia, or these in various combinations. The bearing of the theories on the feed-back proposal (Morley, 1970) is conjectural. Does feedback control the rhythm or the reverse? Morley, King-Smith & Stohlman (1970) discussed the matter of haemal periodicity in detail concluding that 'if many systems do show the same principles of control as does haemopoiesis, many periodic diseases may arise in similar fashion'.

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