A CASE OF CYCLIC NEUTROPENIA

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CYCLIC neutropenia or cyclical agranulocytosis is a very rare disease which has been established as a clinical entity only in recent years. It was first described by Leale in 1910 and in 1946 Vahlquist was able to collect reports of five cases and to add a description of a patient under his own care. In 1949 Reimann collected further cases to make a total of sixteen. Although the published reports of cases are so few, it is remarkable how similar are their main features, there having been episodes of neutropenia, associated frequently with infections and occurring at intervals of approximately twenty-one days. One of the cases comprising Reimann's collection was mentioned on the basis of a personal communication from one of us, and it is the purpose of this paper to give a full report of this case, in which the syndrome started at the age of 7½ months and continued till the patient died at the age of 8 years.

CASE HISTORY

The patient was first seen by us in July 1948, when she was aged 7 years. The details of the child's history were obtained from her mother. She was the first child of healthy, Scottish parents, and her birth weight was 8¾ lbs. (4·0 Kg.). There was no difficulty in the delivery and her mother had been well during the pregnancy. To all appearances the patient was a normal, healthy infant. She was breast-fed until 5½ months old and during this time she grew normally and was well with the exception of a moderate amount of vomiting. At 5½ months she was given Cow & Gate food and breast-feeding was stopped. At 7 months solid foods were introduced into the diet and the vomiting ceased.

At 7½ months her first tooth erupted and it was noticed that the child became ill and that she had shallow ulcers on the tongue and the buccal mucosa. These ulcers remained for about one week and the child's general condition improved when they had healed. Since that time she had been the subject of repeated attacks of fever with ulceration of mucous membranes, usually in the mouth. These attacks had occurred with remarkable regularity, the interval between the onset of consecutive attacks being on an average twenty-one days, with a range of eighteen to twenty-four days. The attacks lasted from one to eight days. Regional lymphadenitis occurred when the ulceration was severe. Systemic effects were sometimes marked and temperatures of 102° F. to 103° F. were not uncommon. On one

occasion there had been ulceration of the rectum and on another of the vagina. No cause had been found and nothing was known to prevent or to abbreviate the attacks.

Since the age of 7½ months it had been rare for the child not to have an attack every three weeks, although some had been so mild that she had not even had to retire to bed. Despite this handicap she had developed into a child of normal size and proportions for her age. She had done remarkably well at school, having kept pace with other children of her age, although she was absent for at least one-third of each term.

Before going to school the only illness which she had suffered in addition to her attacks of fever had been acute bronchitis. Since her first term at school, at the age of 5 years, she had suffered from fairly severe attacks of mumps, measles, German measles, whooping cough, chickenpox and scarlet fever. No history was obtained of asthma, hay fever, urticaria, or any other allergic manifestations.

As might be expected the child had been seen by many physicians and her attacks had been attributed to a wide variety of causes such as scurvy, acidity, allergy and unspecified defects of her teeth and saliva. As a result she had undergone a number of different forms of treatment. She had had her tonsils and adenoids removed and her milk teeth extracted. She had taken ascorbic acid, stilbœstrol, ferrous sulphate, anti-histamine drugs and many other medicaments, but all without any definite effect upon the occurrence or the severity of the attacks.

There had been no history of similar trouble in any other member of her family; nor was there any other serious illness in the family. Her father suffered from a duodenal ulcer but was otherwise healthy. Her mother and her sister, aged 16 months, were both very well indeed.

Description of an Attack of Ulceration

In hospital it was possible to make a detailed study of her attacks, and the following description is of a moderately severe example. On the first day that she was noticed to be unwell she was a little quieter than usual. Her face was pale and a little puffy, the lips in particular being swollen and dry. Her temperature was not raised. On the next day she was in much the same condition but her temperature had risen to 99·5° F. and there was excessive salivation. Some of the saliva ran from her mouth while she slept. On the third day she felt more ill and her tongue was sore but there was no ulcer. By the fifth day ulcers had appeared on the tongue, gums and the buccal mucosa. These ulcers were shallow, with a necrotic base and irregular edges. They measured up to 1·0 cm. in diameter and there was reddening of the mucosa around the ulcers. By the seventh day the attack was at its height. The child was ill with a temperature of 101° F. The mouth was very sore and the breath was foul. There was considerable cervical lymphadenitis, but there was no splenomegaly

and no sign of infection elsewhere in the body. The patient was very well-behaved considering her unpleasant affliction. She remained quiet in bed and required no special attention except that she had to be encouraged to take soft foods on account of the pain in her mouth. She seemed to have become accustomed to these unpleasant episodes and by the tenth day she was bright and cheerful and felt quite well, but the ulcers were not completely healed until the eleventh day.

Examination

Examination of the patient between attacks of fever showed that she had grown to a normal size for her age and that she was of good intelligence. General physical examination revealed no evidence to suggest that she was other than an ordinarily healthy child. Her height was 50 inches; her weight was 52 lbs. and her proportions were normal. The state of her nutrition was excellent. There was no clinical evidence of disease of the nervous, respiratory or cardio-vascular systems. She had neither hepatomegaly nor splenomegaly and there was no lymphadenopathy. Her fæces were normal and her urine contained no abnormal constituents, had a specific gravity of 1·020, was normal in quantity and was usually acid. There were no signs of endocrine dysfunction. X-ray examination of the skull and of the chest showed no abnormality and the bone growth at the wrists and elbows was found to be normal for her age.

The glucose tolerance test was normal on three occasions. Twenty-two gms. of glucose were given by mouth and capillary blood was estimated by the method of Hagedorn and Jensen. An example was :—

Fasting blood sugar . . .	92 mgm. per 100 ml.
60 mins. after glucose . .	182 mgm. per 100 ml.
90 mins. after glucose . .	120 mgm. per 100 ml.
120 mins. after glucose . .	92 mgm. per 100 ml.

Water excretion tests showed a normal diuresis.
The blood urea nitrogen was 18 mgm. per 100 ml.
The blood uric acid was 3·5 mgm. per 100 ml.
The blood Wasserman reaction was negative.

During the attacks her blood sedimentation rate was raised. The maximum recorded was 37 mm. in one hour by the Westergren method. Between the attacks it fell to normal levels. Throat swabs during an attack gave rise to growths of pneumococci and of non-hæmolytic streptococci on culture. A blood culture was negative.

Hæmatological Findings

In the peripheral blood *between* the periods of infection there was a constant neutropenia, the highest figure recorded for the neutrophil count during her stay in hospital being 1900 per cu.mm. Apart from

this there was no other abnormality. A typical count during an interval was :—

Red blood cells	4·5 M. per cu.mm.
Hæmoglobin	86 per cent. (Sahli)
Colour index	0·95
Platelets	205,000 per cu.mm.
Total white cells	4,000 per cu.mm.
Neutrophils	960 per cu.mm.
Eosinophils	80 per cu.mm.
Basophils	40 per cu.mm.
Lymphocytes	2,560 per cu.mm.
Monocytes	320 per cu.mm.
Türck cells	40 per cu.mm.

During the attacks definite changes took place in the differential count of the white cells. The neutrophils fell to very low levels or disappeared altogether. In only one attack was an alteration in the eosinophil count noted and on this occasion the number rose to about 500 cells per cu.mm. There was a constant fall in the lymphocyte count to levels between 1000 and 2000 cells per cu.mm. There was a considerable monocytosis, the monocyte count rising as the neutrophil count fell, and falling again as the neutrophils reappeared in the peripheral blood. At the peaks of the monocytosis there were between 1700 and 2600 of these cells per cu.mm. The neutrophils and lymphocytes started to fall several days before an attack began, while the monocytosis developed during the attack.

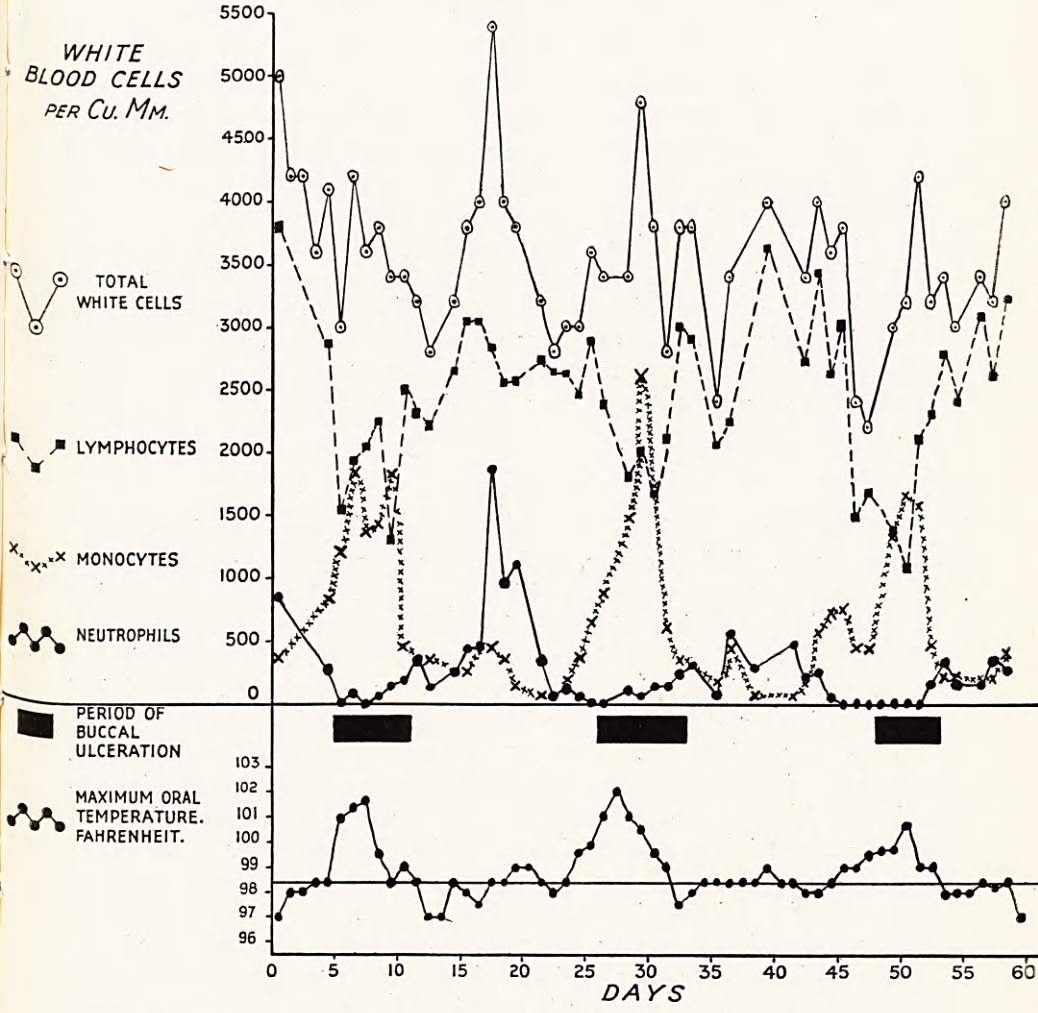
Sternal Marrow

A specimen was obtained during an attack. The red cell precursors were abundant and belonged to the normoblast series with normal maturation. The neutrophil granulocyte series showed a marked maturation arrest at the promyelocyte and myelocyte level. Eosinophil leucocytes and myelocytes were increased in number. Megakaryocytes were normal both in quantity and quality. The lymphocytes were numerous but probably not out of proportion to the number frequently found in the marrow of a child of 7 years.

Endocrine Features

The analogy between cyclical attacks of this sort and the menstrual periods is so obvious that it seemed reasonable, as it had done to others, to investigate the possibility of a connection between endocrine dysfunction and the neutropenia. Thompson noted that in seventeen out of eighteen young women with agranulocytic angina the symptoms had come on within a day or two of the onset of the menstrual period. It has been suggested by subsequent workers that this association was due in reality to the taking of analgesic drugs, including pyramidon, for pre-menstrual pains. He also examined the excretion of œstrogens and of gonadotrophins in the urine of the first case of cyclic neutropenia to be described and found that both were increased in quantity during

the neutropenic phases. This latter finding was not substantiated in the case described by Imerslund. Thus, though there was neither history nor the clinical finding of any abnormality to suggest endocrine disease, it was considered to be worth while to estimate the excretion of œstrogens and of gonadotrophins in the urine.



The œstrogens were estimated for us by Dr Clayton by the Kober reaction and were found to be 0·9 mgm. and 1·2 mgm. per twenty-four hours in the urine on two occasions during an attack of neutropenia with buccal ulceration. These figures were considered to be within normal limits.

The gonadotrophins were estimated for us by Dr Loraine on twenty occasions, during and in between three bouts of neutropenia. The estimations were made upon the basis of the biological effects produced on the prostate, uterus and ovary of rats injected with concentrated

extracts of the patient's urine. The findings by these three methods were in agreement. No evidence of cyclical variation in the rate of gonadotrophin excretion was observed. An excessive secretion of gonadotrophin hormones was only found during one attack. In no other respect was evidence obtained that endocrine factors played an important part in the pathogenesis of the disease.

Fate of the Patient

As it was not possible to find the cause of her disease it was not possible to offer any radical treatment to the patient and she received only suitable symptomatic and local treatment during the periods of buccal ulceration. It was considered that it would be wise to reserve antibiotic therapy for use in neutropenic phases with more than the usual degree of infection. Unfortunately the child died whilst at home, having been discharged for the Christmas and New Year holidays. Apparently she had an attack of ulcers in the mouth at the expected time and of no greater severity than usual, but she had a gross hæmatemesis and died suddenly. There was no autopsy but it seems that there must have been ulceration of the gastric or œsophageal mucosa with involvement of a blood vessel.

Discussion

There can be no doubt that this case was an example of a definite, though rare, clinical entity, and probably more cases will come to light as knowledge of the condition is spread. The most perplexing problem in connection with the disease is that of its aetiology. This question has been discussed at some length by other writers but without definite conclusions being reached. Neither the history, the clinical examination or the laboratory investigations carried out during the study of our patient threw any light on the nature of the disease process.

One point in the hæmatological findings deserves emphasis. In this case there was a neutropenia even between the attacks of ulcers. In fact the highest count of neutrophils observed over a period of two months was one of 1900 per cu.mm. There is no doubt that there was a cyclic variation in the neutrophil count, but rather than there being a normal count with regular falls to low levels, there was persistent neutropenia with regular periods of relative or complete absence of neutrophils. Such a finding is mentioned in the records of at least two of the cases collected by Reimann.

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