RECURRENT NEUTROPENIA

BY

ALAN MONCRIEFF

From the Institute of Child Health and The Hospital for Sick Children, Great Ormond Street, London

The occurrence of periodicity in disease processes has long fascinated medical writers. From Galen to Sydenham there is a long list of contributions which are particularly devoted to the relation of bodily disorders to solar or lunar periodicity. In more recent times periodical endocrine variations have naturally received attention, but scientific proof is lacking for most of the theories put forward, and the general conclusion reached is that there may well be some universal but, as yet, undetected physiological cycle in the human subject. In children the well-known cyclical vomiting syndrome is an example of periodic disease. This together with other related disorders has been well discussed by Wyllie and Schlesinger (1933). Their paper, however, on the periodic syndrome does not give details of blood examinations. The literature contains about a score of cases with periodic decreases in the polymorphonuclear cells of the blood, associated with various other manifestations such as stomatitis and septic infections of the skin. The following case summary concerns an example of this recurrent neutropenia.

Case Report

K.H., a boy, born October 12, 1947, was admitted to The Hospital for Sick Children, Great Ormond Street, on December 3, 1949, at the age of just over 2 years for recurrent febrile attacks, vomiting, and loss of appetite. His parents were unrelated and healthy, and there was no familial illness. He had two older sisters, both healthy. He was born at full term after a normal pregnancy and labour, weighing 7½ lb. His mother 'had no milk' so he was bottle fed, with vitamin supplements, and gained weight satisfactorily. The sole unfortunate episode of his infancy was a severe attack of whooping cough when he was only 1 month old which left him with a cough from which he suffered from time to time. Six months before admission, at the age of 18 months, just as he was starting to walk, he developed acute bronchitis which was treated with sulphathiazole, of which he received 5 g. in all, and an expectorant mixture. He did not recover completely, and had further attacks of cough, fever, listlessness and loss of appetite during the next three months. In one of these, about three months before coming to The Hospital for Sick Children, he was admitted to a local hospital in Surrey where his throat was found to be inflamed; he had a fever up to 103° F., and a blood count showed only 1,000 polymorphonuclear cells out of a total white cell count of 6,000 per c.mm. He was treated with penicillin for five weeks in all, and the infection slowly cleared up, but the polymorphonuclear cells fell lower to a minimum of 100 per c.mm. and he was treated with pentnucleotide. The neutrophil cells rose to 4,000 but had fallen again to 1,500 at the time of discharge.

On admission to The Hospital for Sick Children he had a fever of 103° F., was flushed, with some circumoral pallor, and the principal abnormality found on physical examination was a pair of much enlarged tonsils, covered with a mucoid exudate. There were no physical signs of disease in the lungs or elsewhere. The lymph glands of the neck (or elsewhere) were not enlarged nor was the spleen palpable. A white cell count the day after admission showed a total of 4,300 cells per c.mm. of which 16%, or 700, were polymorphonuclear. Examination of the bone marrow by Dr. I. A. B. Cathie four days after admission gave the impression of marrow cell hypoplasia without evidence of leukaemia. In view of the neutropenia, and the fact that the child was amazingly cheerful despite his tonsillitis, no treatment was given and the temperature fell to normal after one week in hospital. Three days later fever recurred but without any fresh symptoms. The cough recurred and there were a few signs in the lungs of bronchitis. At the onset of this bout the total white cell count was 6,500 per c.mm. with 67% or 4,000 polymorphonuclears. Four days later he was much worse with high fever up to 103° F. with more evidence of acute bronchitis together with a lot of thick, sticky mucus about the whole of the upper respiratory tract. The total white cells were now 3,300 per c.mm. with only 24%, or 800, polymorphonuclears representing a remarkable drop in three days. A throat swab showed on culture a mixed growth of Streptococcus viridans, N. catarrhalis, and diphtheroids. Penicillin by intramuscular injection was started. Two days later his temperature was lower but the white cells were now only 2,950 per c.mm. with the polymorphonuclears 32%, or 950. Nine days later they were lower at 20%, or 600, in a total white cell count of 3,000 per c.mm. Agglutination reactions for the typhoid group and for Brucella abortus were negative. He developed some loose stools, and continued to run a low-grade fever with a cough, but his chest condition slowly cleared. A week later he was much better, without fever, and the white cells had risen to 4,150 per c.mm. with 59%, or 2,500 polymorphonuclears,
and four days later the count was 9,000 per c.mm. with 32%, or 3,000, polymorphonuclears. Four days later again the total neutrophil count was about the same. Then followed another less severe bout of fever and cough with a slight decrease in the total white cell count, the polymorphonuclears keeping about the same. (Fig. 1 shows diagrammatically the fluctuations in the white cell count.)

![Graph showing fluctuations in white cell counts.](image)

Reviewing the whole story it seemed possible that a recurrent respiratory tract infection was the cause of the fever and cough and possibly of the neutropenia. Accordingly, about the beginning of February, 1950, his tonsils and adenoids were removed by Mr. James Crooks. He made a good recovery. There was a slight degree of anaemia for which he was given iron, but on discharge from hospital on February 21, 1950, the white cells were 7,600 per c.mm. with 53%, or 4,000, polymorphonuclears. He has been seen in the out-patient department on several occasions and has had some minor recrudescences of bronchitis but he has continued to gain weight well.

The white cell counts were as follows:

<table>
<thead>
<tr>
<th>Date</th>
<th>Total White Cells</th>
<th>Total Polymorphonuclears</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 24, 1950</td>
<td>5,800</td>
<td>1,260 (39%)</td>
</tr>
<tr>
<td>June 2, 1950</td>
<td>10,100</td>
<td>6,760 (67%)</td>
</tr>
<tr>
<td>October 13, 1950</td>
<td>6,000</td>
<td>3,000 (49%)</td>
</tr>
<tr>
<td>December 8, 1950</td>
<td>10,500</td>
<td>5,900 (57%)</td>
</tr>
</tbody>
</table>

The drop in neutrophils on the occasion of the visit in October was associated with what were called ' festering places on his legs ' which were in fact several small indolent ulcers. Two months later he was quite well again, and has been discharged to the care of his own doctor.

Other investigations in hospital had excluded a urinary tract infection or any abnormal bowel organisms, and a blood culture during the febrile period was negative. X-ray examination of the chest did not show any abnormality. The antra were also clear on examination.

**Discussion**

Agranulocytosis is rare in childhood, certainly as a primary disorder. Secondary decreases in the polymorphonuclear cells may occur with drugs or infections which damage the bone marrow. Sulphonamides, especially in what are termed ' sensitive ' individuals, but also in otherwise normal subjects are well recognized as a possible cause of neutropenia (Whitby and Britton, 1950), but in the present case only one continuous course of sulphathiazole was recorded, and the white cells decreased in hospital when no drug was being given at all. Infection was, however, present at this time and many infections have been blamed for damage to the bone marrow. Blattner (1951) in a short review of vesicular stomatitis suggests that ' the clinical entity of rhythmic neutropenia with recurrent ulceration of the buccal mucosa . . . may prove to be of viral aetiology. ' It is no more easy to explain recurrent infection with a fairly definite and fixed rhythm than to explain the recurrent neutropenia, and it may well be that it is the decrease in the polymorphonuclear cells which comes first and allows the infection to develop. That the fundamental lesion lies in the blood changes is strongly suggested by the long history in some of the cases in the literature. The fluctuations in the white cell counts noted in the present patient after he left hospital and after an obvious focus of infection had been eliminated also suggests that infection is a secondary element in this condition.

One of the most fascinating examples of recurrent neutropenia in the literature has been followed from infancy to death in adult life. The story begins with a paper in 1910 by Leale describing an example of recurrent furunculosis in an infant with an abnormal blood picture. This picture was in fact that of a leucopenia with only 1% of polymorphonuclears on several occasions. Aphthous stomatitis and fever are also mentioned. Twenty years later the same patient is described by Rutledge, Hansen-Prüss, and Thayer (1930). He was then 19 years of age and had
continued to have attacks at three weekly intervals of stomatitis, swelling of the lymphatic glands, and fever. The leucocytes usually numbered, during the bouts, only 2,000 to 4,000 per c.mm. with 6 to 16% of polymorphonuclears. The next and final reference to this patient is given by Thompson (1934). The three-weekly cycle had persisted until death. What was interesting now was that the patient had developed diabetes insipidus and in consequence a fluctuation in the secretion of some hormone was postulated as the inborn error in his physiological constitution.

This same theory of a primary endocrine disorder is discussed by Borne (1949). In describing a girl with cyclic neutropenia at three weekly intervals associated with fever, gingivitis, otitis, and furunculosis dating from 5 months of age and of two and a half years' duration, he records investigations of the female sex hormone. Oestrin was found in the urine just before the onset of the neutropenia. Then, as the neutrophils began to disappear, only a trace of oestrin could be found in the urine, and five further determinations during the cycle failed to detect even a trace of oestrin. Administration of stilboestrol and of progesterone seemed to suppress the neutrophils. Whatever may be the significance of this, however, Borne thinks the primary disturbance is in the bone marrow. ‘Fluctuations in the peripheral blood,' he writes, 'were essentially a reflection of the marrow cytology.’ But Doan (1932), in a much earlier review of the whole subject under the title of 'The Neutropenic State' in mentioning briefly the condition of 'chronic regularly recurring neutropenia,' thinks it is probably not of bone marrow origin, mainly because the neutropenia is unaffected by administration of the pentose nucleotides.

Another mention of the possible relationship of the condition to endocrine disorders or to the endocrine cycle is made by Embleton (1937) in describing a case of rhythmical neutropenia with buccal ulceration in a woman of 43 years of age. The cycle here was either 17 or 36 days and had no relation with the menstrual cycle.

Reimann has written extensively on the subject of periodic disease, a term which includes recurrent attacks of fever and abdominal pain in some patients, myasthenia in others, arthralgia in others, and neutropenia in others. In 1948 he described a patient aged 20 years with repeated episodes of leucopenia and ‘disability’ which consisted of malaise, headache, sore throat, and aching pains all over. This occurred while the polymorphonuclear cells were dropping in number. Small ulcers of the tongue and buccal mucous membrane developed together with some tenderness and swelling of the anterior lymphatic glands in the neck. The symptoms and signs gradually abated while the neutrophil cells increased in number. In a later paper (Reimann, 1949) he has collected more examples as well as other types of fluctuation in the blood cell elements leading to recurrent purpura, for example. Reimann and de Berardinis (1949) have in a third contribution collected 16 examples of cyclical neutropenia associated with fever. Nine of these began in infancy and two between 5 and 12 years of age. Ten were in males. The remarkable feature was the periodicity which was regular at three-weekly intervals and appeared to continue throughout life. Splenectomy, performed in six cases, seemed to help in four and do no good in two. Causation is regarded as still obscure. Until further knowledge is available, states Reimann, it is simplest to regard periodic disease as a manifestation of the rhythm of life. The patient here described does not contribute anything to the solution of the problem. His future will be observed with great interest.

Summary

A boy aged 2 years appeared to suffer from recurrent reductions in the polymorphonuclear white cells, associated with fever and infection. Various theories have been advanced to account for this periodic neutropenia. None of them appears to explain the phenomenon.

References

—— (1949). Ibid., 141, 175.