The Effect of ACTH in Periodic (Cyclic) Neutropenia

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Periodic (cyclic) neutropenia is a chronic disorder of the blood, characterized by the regular recurrence of neutrophilic granulocytopenia, at approximately three week intervals, with secondary constitutional symptoms such as anorexia, malaise, and fever, and secondary infections such as stomatitis, pharyngitis, folliculitis, lymphadenitis, and pneumonitis. Depression of the neutrophilic series of the bone marrow has been demonstrated during the neutropenic periods. Between these periods, the neutrophils return to normal and the patients enjoy good health.

The cases have occurred at all ages, though many have been reported as starting in infancy, and they have had a variable duration, from a few months to as long as thirty-four years. The latter case has been most extensively studied, and papers have been written successively by Leale in 1910, Rutledge, et al. in 1930, Thompson in 1934, and Reimann in 1949; the last paper reported that the patient died of pneumonia at age 34. Reimann's review of this and the fifteen other cases reported through 1949 revealed a remarkable clinical similarity of the cases, with cyclic neutropenia at approximately three week intervals, establishing this condition as a specific clinical entity. He suggested that this condition might be a variation of the larger group of periodic diseases, the etiology of which is unknown.

In only one of the sixteen cases was there any evidence of asthma or other allergic manifestations. Skin tests in these patients have been negative, and antihistaminic drugs have had no effect. Splenectomy has caused some amelioration of the secondary clinical effects, or a less striking diminution of the neutrophils, as reported in six cases, but the periodic neutropenia continued with no cures effected. In two cases, there was no clinical or other effect following splenectomy. The spleen was rarely enlarged and the adrenalin test was negative. It is doubtful that hypersplenism is a primary factor, although in some cases with splenomegaly secondary to other conditions such as lymphosarcoma, secondary hypersplenism may aggravate the underlying process.

The possibility of an endocrine dysfunction was first suggested by Minot who saw the case reported by Rutledge. Although the patient was a male, the resemblance of the periodicity of the neutropenic periods to the menstrual cycle of women impressed him, and he suggested that an alteration of the endocrine system might be responsible for the cyclic depression of the bone marrow. Sparse hair and high pitched voice were present, and the patient later developed diabetes.

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Submitted May 11, 1953; accepted for publication June 8, 1953.

The author is indebted to Dr. Robert B. Francis, of Temple University Hospital, who first suggested the diagnosis in this case, to Major Bertram L. Levy, MC, former Chief of the Medical Service, U. S. Army Hospital, Fort Dix, and to Dr. Normal Learner, of Temple University School of Medicine and Civilian Consultant to the Surgeon General, for their helpful suggestions and criticisms.
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insipidus. Extract of anterior pituitary, suggested by Minot, had no striking effect. Thompson, in studying the same patient, found the urinary gonadotropin level to increase and the urinary estrogens to diminish prior to the neutropenic period, as occurs in women prior to menstruation. Reimann and de Berardinis could show no fluctuating levels of these hormones or of the 17 ketosteroids with the cycles of neutropenia in their patient.

The influence of the endocrine system on hemopoiesis has long been obscure. There is considerable evidence, however, that the cortical hormones, like other endocrine secretions, probably exert a potentiating and regulating effect, accelerating or controlling metabolic processes, which may proceed even in the absence of the hormones. Interest in this subject has been stimulated recently by the use of adrenocorticotropic hormone and cortisone in various hematologic conditions. It is not surprising, therefore, that ACTH has been used in periodic neutropenia, with conflicting reports. Reimann and de Berardinis reported no rise in neutrophil count after single intramuscular injections of ACTH during the neutropenic phase. Monto, et al., however, reported "dramatic" clinical improvement and "favorable" changes in the blood and bone marrow in their case.

We were stimulated, therefore, by these reports to use ACTH in the following patient.

CASE REPORT

A 20 year old white male was admitted to the hospital on June 10, 1952, with the symptoms of sore throat, painful sore mouth, productive cough, and fever up to 103°F. He was weak and toxic and ate solid food with difficulty because of the sore mouth and throat.

He stated that he had a rare blood disease dating from the age of 6 months, with frequent recurrences of canker sores of the mouth, sore throat, furuncles, and swollen lymph nodes, and that this was associated with fever, anorexia, and malaise. He had been under the care of several physicians and hospitals, but with no definite diagnosis ever being made. He had the impression that these episodes occurred approximately every three weeks, but that between attacks he felt well. By limiting his activities at the time of his expected attacks, he thought that he could control the severity of the episodes, and have only mild effects without fever or serious infections. Fatigue or excessive physical exertion prior to his period were often followed by attacks with fever, severe sore throat and infections requiring penicillin or sulfonamide therapy. These attacks were also almost always characterized by the occurrence of a painful ulcer somewhere on the buccal mucosa, and examination of the mouth revealed many scars and pits on the buccal mucosa and tongue, from old lesions of stomatitis.

Records from his private physicians and hospitalizations were obtained. In 1935, at the age of 3, he was hospitalized at Children's Hospital, Boston, with the diagnosis of stomatitis herpetiformis. His leukocyte count was 5300 per cu.mm., with 30 per cent neutrophils, 60 per cent lymphocytes, 7 per cent monocytes, and 3 per cent eosinophils. In 1937, at age 5, he was admitted to the Lynn Hospital, Lynn, Massachusetts, at which time the diagnosis of congenital leukopenia was made. He was referred to the Tufts College Dental School because of the recurrent stomatitis, and his leukocyte count then was 3450 per cu.mm., with 1 per cent neutrophils, 75 per cent lymphocytes, 2 per cent basophils, 11 per cent eosinophils, and 11 per cent monocytes. The hemoglobin was 70 per cent and the red blood count 3.8 million per cu.mm. Cultures of mouth and gum lesions revealed normal flora. He was skin tested with antigens for wheat, eggs, casein, and numerous other protein foods and vegetables and no positive reactions were found. In 1945, he was admitted to the Salem Hospital, Salem, Massachusetts, where a biopsy of cervical lymph node was done following the appearance of large tender cervical lymphadenopathy. The biopsy revealed
nonspecific granulation tissue. In 1947, he was readmitted to Salem Hospital with an episode of acute pneumonitis. His leukocyte count at that time was 5200 per cu.mm., with 40 per cent neutrophils, 1 per cent band forms, and 59 per cent lymphocytes. Frequent or daily leukocyte counts were not checked, and a cyclic variation in his leukocyte level was never determined. Bone marrow study was never done. He denied persistent or occasional use of any drugs.

The recurrent stomatitis and other symptoms continued at approximately three week intervals. In spite of this chronic illness, he was able to complete high school. He was always underweight and frail, and developed his interests in art and intellectual pursuits. He had maintained his weight at approximately 118 lbs. for the past two years. In an attempt to build himself up and keep up with his friends, he decided to join the army, not revealing his past history at his induction physical examination.

Physical examination on admission revealed a thin, sickly appearing white male who was acutely ill, toxic, and dehydrated. His height was 5 feet 8 inches, weight 118 lbs., temperature 93 F., pulse 100, blood pressure 100/70. There was no evidence of icterus, unusual pallor, cyanosis, or clubbing of the fingers. The skin revealed scattered pustules and furuncles on the forehead, face, neck, and thighs. There was a normal male distribution of hair, and his voice was of a normal male character. In the mouth, an acutely inflamed ulcer, 1.5 cm. in diameter, was seen on the left buccal mucosa adjacent to the molar teeth, with the surrounding mucosa red and edematous. Many scars and pits of healed mouth ulcers were seen, and the surface and edge of the tongue were irregular and jagged. The throat and tonsils were acutely inflamed, with many patches of yellowish exudate on the swollen tonsils. The neck was supple with moderately enlarged tender anterior cervical nodes. The chest revealed slight funnel-breast deformity, with equal and adequate expansion. The lungs revealed areas of bronchial breathing and many diffuse medium and fine rales throughout both lung fields. The heart was not remarkable, the rate 100, and the rhythm regular. Abdominal examination was not remarkable and the spleen was not palpable. The genitalia were well developed and there was no testicular atrophy.

Laboratory data on admission revealed a white blood count of 1300 per cu.mm., with 0 per cent neutrophils, 98 per cent lymphocytes, and 2 per cent eosinophils. The hemoglobin was 13.5 Gm. per 100 cc., the hematocrit 37 per cent, and the red blood count 4.6 million per cu.mm. The reticulocyte count was 0 per cent, platelet count 190,000 per cu.mm., bleeding time 2 minutes and 40 seconds, and the coagulation time 20 minutes (Lee-White). Urinalysis revealed 2+ albuminuria, occasional WBCs and a specific gravity of 1.020. Repeat urinalyses showed clearing of the albuminuria and cellular elements, and were within normal limits. Throat culture on admission revealed a heavy growth of Beta hemolytic streptococcus, and sputum culture revealed moderate growth of pneumococcus. The serum protein was 6.5 Gm. per cent, with albumin 3.6 Gm. per cent and globulin 2.9 Gm. per cent. The cardiolipin microflocculation reaction was negative. The heterophile antibody titer was elevated to 1/14 dilution on admission, but no subsequent rise in titer occurred. Blood cultures were sterile.

On the second hospital day, the leukocyte count was 1350 per cu.mm. with 19 per cent neutrophils, 66 per cent lymphocytes, 4 per cent monocytes, and 11 per cent eosinophils. Daily leukocyte counts and differential counts were done throughout his four month hospital course (see fig. 1, the graph of daily total neutrophil counts). In general, the graph shows the greatest depression of neutrophils on June 10 and 30, July 23, August 12 and 23, and September 13. During these neutropenic periods, the leukocytes varied from 1300 to 4600 per cu.mm., with 0 to 30 per cent neutrophils, and 3 to 13 per cent eosinophils, with the remainder as lymphocytes or monocytes. There was an inverse relationship between the neutrophils and eosinophils, the latter increasing when the former decreased.

A bone marrow aspiration biopsy was done on June 10, 1952 during the maximum depression of circulating neutrophils and revealed a uniform diminution of the neutrophilic series, with a moderate increase in the eosinophils and lymphocytes, and a slight decrease in the myeloid-erythroid ratio. On June 21, with return of the peripheral neutrophil count to normal levels, the bone marrow revealed hyperplasia of the neutrophilic series with an increase in the neutrophilic myelocytes and juvenile forms, with an increase in the myeloid-erythroid ratio, and with no abnormal forms seen. During the neutropenic periods, the
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Fig. 1.—Daily total neutrophil count correlated with occurrence of fever and stomatitis. The periods covered with penicillin and ACTH are charted. Note lack of response of neutropenia to ACTH.

sedimentation rates (Wintrobe) were elevated. The remainder of the hematologic studies, including hemoglobin, hematocrit, red blood counts, platelet counts, tourniquet test (Rumpel-Leede), clot retraction time, bleeding, clotting, and prothrombin time, were all within normal limits. An adrenalin test was done during a neutropenic period, with leukocytes counted 5, 15, 30, and 60 minutes after the injection of 0.5 cc. of adrenalin 1:1000 subeutaneously; it revealed no change or increase in the total leukocyte count or differential.

Chest x-ray on admission revealed soft patchy infiltrations irregularly distributed throughout both lung fields, having an appearance “suggestive of the picture of Loeffler’s syndrome.” This cleared completely one week later. During three successive episodes of neutropenia, chest x-rays remained completely negative. Abdominal films failed to reveal any enlargement or change in the size of the spleen.

Hospital Course

On admission the patient was acutely ill with agranulocytosis and secondary severe stomatitis, tonsillitis, and pneumonitis. He was given parenteral fluids and penicillin 100,000 units every six hours for forty-eight hours, and then 300,000 units twice daily until June 23. A daily chart of his leukocyte count revealed return to normal levels by June 17, when the patient was afebrile and the chest x-ray was clear. The mouth and throat lesions had also cleared. On June 26, the neutrophil count again dropped sharply, he developed a fever of 102 F., and he again complained of sore throat. Examination revealed diffuse inflammation of the throat and tonsils, for which he was again treated with penicillin. He again improved and his neutrophil count returned to normal levels by the 4th of July and he felt perfectly well until his next period which began on July 18, with a fever of 101 F. and a painful red ulcer on his tongue. This lasted approximately five days, and as his neutrophil count again rose to normal levels, he felt better.

On August 5, his neutrophil count again dropped to subnormal levels, and ACTH, 10 mg. in a liter of 5 per cent dextrose in water, was given intravenously by slow drip over a ten hour period, and this was continued for six days. At the onset, his leukocyte count was 4400 per cu. mm., with 0 per cent neutrophils, 89 per cent lymphocytes, and 11 per cent eosinophils, and his daily counts showed a continued down-grade during the ACTH administration, remaining at agranulocytic levels for five days. The total eosinophil count dropped from 150 to 50 per cu. mm. after ACTH. There was no effect on the neutropenia, but this period was unusual because of the absence of accompanying stomatitis or other secondary manifestations.

In spite of the ACTH, the next period occurred on schedule on August 22, associated with
reappearance of stomatitis. It was decided to try ACTH with his next period, but this time it was started while he was in remission, and the dose of ACTH was increased to 25 mg. administered in the same manner as previously, so as to preclude the possibility of insufficient dosage for maximal adrenal response. However, two days after the onset of the ACTH administration, his neutrophil count began its downward trend and in the midst of ACTH therapy dropped to 2900 leukocytes per cu. mm., with 1 per cent neutrophils and 99 per cent lymphocytes. ACTH was continued for six days with no effect on the neutrophil count. The total eosinophil count dropped from 150 cu. mm. to 0. It was noted again that this period was free of associated secondary manifestations such as stomatitis or pharyngitis, in spite of absence of antibiotic medication.

**DISCUSSION**

This case, with periodic recurrences of fever, stomatitis, pharyngitis, lymphadenitis, furunculitis, and pneumonitis, associated with depression of the neutrophilic granulocytes at intervals of approximately three weeks, fits the clinical description of the entity described by Reimann⁷ and called periodic neutropenia. During a seventeen week hospitalization he was observed through six episodes of neutropenia, occurring at intervals from fifteen to twenty days.

Adrenocorticotropic hormone and cortisone have been used with beneficial effects in various hematologic disorders such as hemolytic anemia, thrombocytopenic purpura, acute leukemia, and other related conditions.⁹ In studying such cases, Wintrobe noted stimulation of the granulopoietic tissue as manifested by neutrophilic leukocytosis in thirteen of sixteen cases treated with ACTH, in addition to improvement of anemia or thrombocytopenia for which the ACTH was given.

Reimann and de Berardinis⁷ gave single 25 mg. intramuscular injections of ACTH to their patient during the interim between cycles of neutropenia as well as during the neutropenic phase. They observed, during the interim between cycles, that the leukocyte count remained constant but the percentage of neutrophils rose. During the phase of neutropenia, after the leukocyte count fell from 4000 to 2000, a further decrease in the neutrophils occurred after ACTH.

Monto, et al.⁵ showed a rise in leukocyte count from 600 or 700 cells to 1650 cells per cu. mm., with 67 per cent neutrophils, seventy-two hours after ACTH administration. A bone marrow examination made six days after ACTH therapy revealed a hyperplastic marrow with a marked increase in the number of cells of the granulocytic series. Clinical improvement was described as dramatic, but before additional cycles occurred, splenectomy was done, which relieved, but did not eliminate, the neutropenic cycles.

We found that a typical rise in neutrophil count which occurred spontaneously at the end of a neutropenic cycle was often from 0 to 4500 neutrophils per cu. mm., without preceding ACTH. The rise in neutrophil count noted by Monto⁵ seventy-two hours after ACTH could have been the normal rise at the end of the neutropenic cycle, without attributing this rise to the ACTH. The bone marrow, in our case, also showed a hyperplasia of the neutrophilic elements at the end of the cycles, without preceding ACTH. ACTH administered intravenously according to the method described by Renold, et al.,⁴ sufficient to cause maximal adrenal response, showed no effect in raising the neutrophil count during severe neutropenic cycles, and we were not impressed that it had enhanced the rate of increase of neutrophils at the end of the neutropenic phase.
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The first course of ACTH was given two days after the neutropenic cycle started, and the neutrophils continued to drop to agranulocytic levels in spite of six days of therapy, and there was no abrupt or pronounced effect at the end of the cycle. The next neutropenic cycle occurred on schedule approximately three weeks later. ACTH, 25 mg. intravenously, was then given while the neutropenia was in remission, but two days later, and during the ACTH administration, the neutrophils dropped again to severe neutropenic levels. It is noteworthy, however, that the periods covered with ACTH were not associated with stomatitis, fever, or other secondary manifestations.

We had planned to study urinary gonadotropins and estrogen excretion during the neutropenic cycles to confirm Thompson's report of a cyclic alteration of these hormones as in menstruating women. However, the patient refused further studies. An attempt to prevent the cyclic variation of these hormones by maintaining these levels by exogenous administration might serve as another means of treating this condition.

The ineffectiveness of ACTH in this case further substantiates the prediction of Wintrobe concerning the effect of hormones in hematologic disorders. He stated that, "except where hormone administration meets a deficiency, as in hypothyroidism and in Addison's disease, one should observe only temporary benefits . . . inconsistency in clinical response . . . and escape from effects achieved."

SUMMARY

A case of periodic neutropenia of twenty years' duration is presented. ACTH was administered intravenously in an attempt to abort or prevent the neutropenic cycles. No effect in raising the total leukocyte or neutrophil count was noted, and the neutropenic cycles could not be prevented by the ACTH. A striking absence of fever, stomatitis, or other secondary manifestations occurred during the neutropenic periods treated with ACTH. The background for treating such conditions with hormones is discussed.

SUMARIO IN INTERLINGUA

Un caso de neutropenia periodic de un duration de vinti annos es presentate. Administration intravenose de ACTH esseva empletate in le spero de facer abortar o de prevenir le cyclos neutropenic. Nulle effecto in aitlar le conto total de leucocytas o neutrophilas esseva constatatate, e le cyclos neutropenic non poteva esser prevenite per medio de ACTH. Un frappante absentia de febre, stomatitis, e altere manifestationes secundari esseva notate durante le periodos de therapia a ACTH. Etiam le conditiones governante le tractamento hormonic de tal casos es discutite.

REFERENCES

BERNARD H. CHAIKEN

The Effect of ACTH in Periodic (Cyclic) Neutropenia

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