

CHRONIC INFECTIOUS MONONUCLEOSIS

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IN A GROUP of 206 patients who had infectious mononucleosis, 53 had some symptoms which persisted for from three months to at least four years or longer. The syndrome included ease of fatigue, exhaustion, aching of the legs, weakness, depression, afternoon elevation of temperature (99.8 to 101 F.), moderate splenomegaly, low blood pressure, low blood sugar, often low specific gravity of the urine, and the presence of infectious mononucleosis cells in the blood.

The 53 patients with the chronic symptoms included 22 males and 31 females. The ages ranged from 8 months to 60 years. There were 5 younger than 19 years; 20-29 years, 12; 30-39 years, 16; 40-49 years, 15; 50-60 years, 5. The 8 month old child showed unusual diarrhea ("dysentery") since birth, and examination of the blood showed infectious mononucleosis cells. The mother had acute infectious mononucleosis during pregnancy, one month before the birth of the child. Thirteen of the patients had the symptoms for from 3 to 6 months; 15 for 7-12 months; 3 for 17-18 months; 11 for one year; 8 from two and one-half to four years and 3 for at least six years. Some of the patients could give the exact date of the start of the symptoms, others within a month or so. Five gave the duration as "several months," "several years," "many years."

These patients had been sent in for study, with possible diagnoses of undulant fever, tuberculosis, Addison's disease, Hodgkin's disease, Rocky Mountain spotted fever, lymphosarcoma, hypothyroidism, menopausal syndrome, subacute bacterial endocarditis, neurasthenia and syphilis.

All of the group showed infectious mononucleosis cells in the blood. The red blood cell and leukocyte counts and hemoglobin content were within normal limits. The infectious mononucleosis cells were of the mature type, with deeply basophilic cytoplasm, staining the peculiar blue characteristic of these cells. The nuclei showed the streaky chromatin, with fenestrations, and were often indented. Occasionally one or more of the large forms found in the acute type were noted. The cells constituted 1 to 7 per cent of the total leukocytes, rarely higher. These cells had been grouped with the lymphocytes or monocytes by uncritical technicians.

In no case of the chronic group was the sheep cell (heterophile) agglutination titer above 1:64. Five patients showed persistent "positive" Kahn tests, characterized as "general biologic reaction," for one to six years.

The presenting symptom was always weakness or ease of fatigue. The patients said that their legs were weak and ached. The fatigue was usually present on arising in the morning, but occasionally developed late in the morning or during the afternoon. Some had symptoms suggestive of hypoglycemia. Others had mental depression, nervousness, ease of perspiration and dizzy or giddy spells on arising.

The fatigue appeared out of proportion to the physical data. The usual findings

were a slightly enlarged spleen, about 14 to 16 centimeters, occasionally palpable on deep inspiration, depending on the patient's body-build. The spleen could be outlined by direct percussion (not by the intermediate method) by using very light tapping. It could be demonstrated by x-ray examination. The enlarged spleen elevated the cardiac apex, while the patient was lying down, so that the cardiac tip was from 10 to 11 cm. to the left of the midline. On standing the apex lowered to about 9 cm. to the left of the midline.

The second feature noted in most of the patients was the comparatively low blood pressure. The systolic figures were from 90 to 105, occasionally as high as 115, with diastolic pressures of 56 to 70. This was significant, as most of the patients belonged to the older age group. There were no definite signs of myocardial or circulatory insufficiency, and there was usually no edema of the ankles.

In most of the patients who made observations on their temperature, there was an afternoon rise to 99.6–101.4 F. Rarely was it higher than this, but in some the elevation was so persistent that they had been diagnosed "fever of unknown origin" or were suspected of having undulant fever, Hodgkin's disease or tuberculosis.

Most of the patients had some lymph nodes which were palpable, but never very large. Enlarged posterior cervical nodes were the most common. In many, the nodes were well within normal limits of size.

A number of patients had symptoms suggestive of hypoglycemia. Late in the morning there was a feeling of exhaustion, anxiety, increased perspiration. The blood sugar (fasting, after food, and at intervals after sugar ingestion) was observed in ten individuals. The fasting blood sugar showed levels of 33 to 70 mg. per 100 cc. using a method in which most normal individuals showed from 80 to 110 mg. per 100 cc. Isolated observations on other patients in the group showed levels of 80 to 95 mg. per 100 cc. After ingestion of a meal or a measured amount of glucose, there was but slight increase in the height of the glucose curve (increased tolerance), and the fall was slow, although 3 individuals showed a lower level than the fasting level between three and five hours after the ingestion of the glucose.

The serum sodium, potassium and chlorine was within normal limits in these patients. None of the patients showed unusual pigmentation.

In 12 of the patients, low basal metabolic percentage had led their physicians to prescribe thyroid, without therapeutic advantage, however, as the abnormal fatigue persisted.

The only feature of the urine which was present in most of the individuals was a low specific gravity of individual specimens taken at random during the morning or afternoon. Values from 1.001 to 1.008 were common, and values higher than 1.010 were unusual in this group.

In 3 patients of the group being studied, although the onset was typical of acute infectious mononucleosis, material from lymph nodes had been obtained by biopsy. The sections were variously interpreted by different observers, and x-ray therapy was given over all the glandular areas by the patients' doctors. These patients later

had a recurrence of the glandular enlargements, and one was diagnosed as lymphosarcoma, one reticulum cell sarcoma and one Hodgkin's disease. They continued to show clear-cut infectious mononucleosis cells in their blood. The "lymphosarcoma" patient received intensive x-ray irradiation from several doctors, as well as "nitrogen mustard" until he died of emaciation. The results make one wonder if lymph nodes, injured or made more susceptible by infectious mononucleosis, may be made to show "malignant" characteristics after x-ray therapy.

In another group, 2 patients showed progressive enlargement of the spleen and were later classed as "Banti's disease." It is possible that some congestive splenomegalies may arise in this way.

In the differential diagnosis, undulant fever presents the most difficult problem. The various tests for degrees of immunity are not diagnostic of the disease, and a positive blood culture is not easily obtainable in the chronic form. The presence of infectious mononucleosis cells in the blood is a differential point, although an individual could have had both diseases. When the Kahn test was positive in these patients, it was of the "general biologic" type.

TREATMENT

Many therapeutic agents were tested without success. These included caffeine, amphetamine sulfate (benzedrine and dexedrine), strychnine, thiamine, atropine, multiple vitamin mixtures, thyroid, ephedrine and special diets. These substances produced no lasting effect, and often accentuated the nervousness. The most promising medicine appeared to be a preparation of adrenal cortical extract (cortalex). This was given in doses of 2 tablets (made from aqueous extract of 10 grams of adrenal gland) on arising in the morning. There was but little subjective improvement during the first week, but a definite feeling of well being developed during the second week and was quite definite during the third week. After this the medication was discontinued and the improvement usually continued. In a few patients it was necessary to increase the dose, or resume it after its discontinuance. Associated with the subjective improvement, there was a decrease in the size of the spleen. The changes in the blood pressure were slight.

The fact that the symptomatology is somewhat suggestive of adrenal insufficiency of the Addison's disease type, and that administration of adrenal cortical extract by mouth relieved the patients after the symptoms had persisted for long periods, suggests a possible mechanism for the fatigue during the chronic stage. There are apparently no data on the appearance of the adrenal cortex in this condition, and whatever damage is present must be reversible, if adrenal insufficiency is the cause of the symptomatology.

SUMMARY AND CONCLUSIONS

A group of patients is described in whom ease of fatigue, fever, splenomegaly, low blood pressure, low blood sugar, low specific gravity of the urine and the presence of infectious mononucleosis cells in the blood persisted for from three months to longer than four years after the initial attack.

Three of the group developed characteristics of lymphoblastoma and two showed the features of Banti's congestive splenomegaly.

The symptoms responded to treatment with a preparation of adrenal cortical extract.

The syndrome is apparently not uncommon and the intense, prolonged debility, together with the marked improvement after therapy with adrenal cortical extract, makes its recognition of great practical importance.