A CASE OF PRIMARY AGRANULOCYTIC ANGINA

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In view of its comparative rarity, we feel that it is worth while reporting the following case, which was treated by continuous intramuscular drip pentose nucleotide and oral sodium nucleinate.

Case Record

A married fitter aged 30 was first admitted to hospital on May 27, 1943, with a history of pains in the knees, ankles, and the left elbow, wrist, and fingers of five days' duration. He was a moderate drinker and smoker. The previous history included an attack of rheumatic fever at the age of 7.

On examination his temperature was 100° F. (37.8° C.), pulse 80, respiration 22. He looked pale, but had no other gross physical signs. The urine was normal; the blood sedimentation rate was 78 mm. in one hour. He was thought to be suffering from acute rheumatism, and was given salicylates, with little or no effect. On June 1 an ulcer of the gum was noted, and three days later several more had appeared, with a lymphadenitis of the deep cervical glands. The white cell count was 2,400 per c.mm. (neutrophil polymorphs 17%, lymphocytes 69%, and monocytes 14%). Haemoglobin and red cell count were normal. He was given 10 ml. of pentose nucleotide daily for three days, after which the white cell count remained the same, but the neutrophils had risen to 28% and there were 2% myelocytes. On June 11 he was feeling better, the ulcers had gone, and he was afebrile, but the white cells had dropped to 1,900 per c.mm. (neutrophils 22%, lymphocytes 69%, monocytes 9%). Pentose nucleotide, 60 ml. daily, was given for three days, and on the last day he was transfused with a pint of Group B whole blood, three days old. On June 14 there was no change in his total white cell count, and a marrow puncture gave the following result:

Cell Type	%	Range of Normal Values (%)
Pro-erythroblasts	4.0	0-4
Erythroblasts	16.5	2-7
Normoblasts	1.0	7-19
Mature polymorphs	13.5	20-50
Basophils	0.5	0-1
Eosinophils	1.0	0-4
Myeloblasts	6.0	0-2.5
Myelocytes	11.0	2-9
Other immature polymorphs (metamyelocytes)	36.5	2.5-14.5
Lymphocytes	10.0	5-20

The patient was anxious to go home and was discharged. The last white cell count was 2,750 per c.mm., neutrophils 17%.

On March 2, 1944, after nine months at home, he was re-admitted with similar symptoms and signs. He was again discharged after being given low doses of pentose nucleotide, the white cell count showing no gross change. He was again admitted on July 14 with a severe recrudescence of symptoms, especially the joint pains. The white cell count was 3,150 per c.mm., neutrophils 46%. At the suggestion of one of our colleagues (Dr. Marchmont) a continuous intramuscular drip containing 40 ml. of pentose nucleotide in 540 ml. of normal saline was given into the vastus externus at the rate of ten drops a minute, and was continued for three days, 120 ml. of pentose nucleotide being given in all. A white cell count then showed a total of 6,700 per c.mm.; the nucleotide was, however, continued by the intermittent method, 10 ml. being given intramuscularly twice daily for three days, and 5 ml. twice daily for a further three days, but the count remained the same. A further 5 ml. once daily for three more days was ordered, and on the completion of this course the white cells numbered 9,500 per c.mm.

Further investigation showed that the haemoglobin percentage, red blood cell count, and platelet count were normal, having remained so throughout his illness. A fractional test meal revealed low acidity, with some delay in emptying of stomach. Biopsy of an axillary lymph gland showed marked reactive hyperplasia of lymph germ-centres and reticulo-synctium.

Between July 31 and his discharge on Aug. 12 no further nucleotide was given, but the white cell count remained around 6,500 per c.mm. On the analogy of the replacement therapy of Addison's anaemia, sodium nucleinate in doses of 1 to 2 dr. (4-8 g.) daily was given, and in the subsequent follow-up at the out-patient department no significant change in the count was noted after ten months. The

oral nucleinate was therefore stopped, and up to the time of writing the count has remained within normal limits.

Discussion

Speculation has been rife on the aetiology of this disease, and many theories have been put forward. Rutledge *et al.* (1930) believe that the condition is a primary disease of the myeloid tissue of the marrow and that the necrotic ulcerations are produced as a result of the neutropenia allowing of bacterial invasion. Osgood *et al.* (1939) quote the normal white cell differential count as follows:

Cell Type	No.	Range %
Neutrophil	1,500-7,500	15-75
Eosinophil	0-400	0-4
Basophil	0-200	0-2
Lymphocyte	1,000-4,500	10-45
Monocyte	0-800	0-8

When our own case was first suspected on June 4, 1943, the patient had 408 neutrophil polymorphs per c.mm. of blood, and the marrow film count, on June 14, 1943, showed a clear majority of young immature cells of the prematuration series, suggesting the maturation rather than the aplastic type of the disease. His relapses in March and July, 1944, suggest a critical level of 1,500 neutrophil polymorphs per c.mm. below which symptoms and signs are observed. Of course, this critical level, below which stomal ulceration may occur, possibly varies from patient to patient. The following case is an example.

A boy aged 10 was admitted with ulcers on the buccal mucosa. The white cell count was 4,600 per c.mm., of which 59% (2,750) were polymorphs and 38% lymphocytes. He had had 12 g. of sulphathiazole. Was he suffering from sulphamide granulocytopenia with a critical level above that of the other case? Whitby maintains that the polymorph counts in children approach the adult level one week after birth. Within eleven days this child's white blood cell count had risen to 9,000 per c.mm., of which 50% (4,500) were polymorphs.

The stimulus which causes granulocytes to enter the circulation is said to be nucleic acid and its derivatives, though its role in maturation is uncertain. Again, pentose nucleotide is said to be useful in both primary and secondary granulocytopenia, the usual method being by daily intermittent intramuscular injections; but though our patient had 105 ml. by this technique his white cell count only slowly improved. A transfusion of a pint of blood made no appreciable difference. However, the value of blood transfusion in these cases is disputed, the only effect, theoretically, being to add nucleotide to the patient's blood by the breakdown of donor leucocytes. Whitby and Britton (1944) state that the total white cell count may actually be lowered as a result of transfusion. It occurred to us that failure may have been due to too rapid destruction of the nucleotide or the overstimulation of the marrow by one massive dose. We therefore thought that a continuous intramuscular drip transfusion, of a total of 120 ml. of nucleotide in saline, at the usual rate of ten drops a minute might be better. The total white cell count rose in three days from 3,150 to 6,700 per c.mm. at a much greater rate than that obtained with the intermittent injections of 105 ml. of nucleotide for a further nine days.

The question remaining unsolved was whether he might recover in any case (as these cases sometimes do). On Jan. 1, 1946, after he had been ten months off sodium nucleinate, his white cell count was 6,400 per c.mm. This would seem to indicate a spontaneous recovery and the uselessness of the oral nucleinate, possibly because, unlike the haemopoietic principle, it never reached the marrow in an unmodified state, it being thoroughly digested in the gut beforehand. Glutathione and liver extract were never given, as the rationale of their use is doubtful, though the haemopoietic principle in the latter has some influence on white cell maturation. The patient gave only a five-day history when first seen, though whether this was really the first attack of his present malady is, of course, debatable. Finally, though neutrophil granulocytes were always present—i.e., the condition was a granulocytopenia rather than an agranulocytosis—we labelled it primary agranulocytosis, as most authorities, such as Wintrobe (1942), Whitby, etc., consider it the term best fitted to cover what is, after all, a very heterogeneous group.

Summary

A case of primary agranulocytosis in a man aged 30 is described, together with a method of treatment by continuous intramuscular drip pentose nucleotide. That recovery was probably spontaneous is discussed in the light of possible treatments.

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THE EFFECT OF *d*-TUBOCURARINE CHLORIDE ON SENSATION IN MAN

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Curare is being increasingly used as an adjunct to anaesthesia. It has been employed widely in America as a biologically standardized extract of curare known as "intocostin," prepared by E. R. Squibb and Sons. It is being used in this country as the active principle isolated by Harold King (1935), *d*-tubocurarine chloride, and is sold as "tubarine."

There seems to be a belief that curare itself has some central depressant action and may thus contribute an analgesic or anaesthetic action of its own when used in anaesthesia. Theoretically this might be possible, as curare is known to block the effect of acetylcholine at ganglia and at the neuromuscular junction; and recent work (Bülbring and Burn, 1941) suggests that acetylcholine is concerned in transmission in the central nervous system. However, experimental evidence on the effect of curare on the central nervous system is confusing.

Von Euler and Wahlund (1941) confirmed earlier reports of an initial central stimulant action on the vasomotor and respiratory centres after intracisternal injection of curare; prolonged action of larger doses caused paralysis of these centres. Intralumbar injection of curare had a strychnine-like effect on spinal reflex excitability. Fegler (1942) showed an initial stimulation of respiration due to curare in anaesthetized dogs, and this may have been central. Other workers (Kahlson and Peil, 1937, in rabbits, for example) obtained respiratory depression. A narcotic effect of curare was reported by Feitelberg and Pick (1942), who performed electroencephalography on frogs. Pick and Unna (1945) later showed that there were separate central and peripheral actions, the former being present when the frog could still jump. Ranyard West (Hartridge and West, 1931; West, 1935) claimed that curare has a "lissive" or rigidity-removing action on dogs in tetany by virtue of a central effect, since this action precedes paralysis of the animal. He also reports respiratory depression appearing before paralysis of the respiratory muscles.

Unconsciousness following the administration of curare to man is described by Whitacre and Fisher (1945), who claim that there was no clinical evidence of hypoxia in these patients, and that there was no period of analgesia preceding the sudden loss of consciousness and muscular paralysis. The two patients described were, however, exsanguinated and shocked. In a third patient, a 72-year-old woman, resection of the colon was performed, using premedication and 405 mg. of "intocostin." The patient was unconscious throughout. In two other patients curare in doses causing marked respiratory paralysis had no analgesic activity, the patients saying later that the pain was unbearable until cyclopropane was administered. Griffith (1945) mentions these results and concludes that, at least in safe doses, "curare is in no sense an anaesthetic agent." Prescott, Organe,

and Rowbotham (1946) made the same observation. Five minutes after the injection of 30 mg. of *d*-tubocurarine chloride the subject was just beginning to lose consciousness. At this time respiratory exchange was inadequate; the "resultant asphyxia was masked by the fact that the subject was breathing pure oxygen." They further report no analgesic action with this dose.

Other workers have claimed that curare enhances the narcotic effect of other drugs (Brody, 1945; Gray and Halton, 1946). Cullen (1944) and Gross and Cullen (1943) point out that ether, "avertin," and sodium thiopentone ("pentothal") have a curare-like action of their own, and this action may explain some of the supposed synergisms.

We have therefore obtained some information on a possible analgesic action of curarine (*d*-tubocurarine chloride, Burroughs Wellcome and Co.) given intravenously in doses which, though small (5 and 7.5 mg.), did cause noticeable weakness of the muscles of the eyes, face, and jaw, and, to a less degree, those of the neck and arms. The effect of each dose has been observed in two men each weighing 10 st. (63.5 kg.). Sensation and cerebation were tested before injection, five minutes later at the height of muscular weakness, and again at fifteen minutes after injection during recovery.

Sensation was tested as follows: touch, with von Frey's hair (0.5 g.); skin pain, with two needles mounted on von Frey's hairs, the heavier giving immediate pain with each prick and the lighter giving no immediate pain but only a delayed sting; deep pain, by pressure over the subcutaneous surface of the tibia with an analgesimeter, the reading in pounds pressure at which pain was felt being noted. Cerebation was tested by mental arithmetic and by the ability to repeat sentences read out by an observer.

After curarine no sensory changes could be detected by these simple tests. The pain threshold was unaltered—15 lb. (6.8 kg.) as against 13 lb. (5.9 kg.) before injection. Cerebation was also unimpaired. For an evaluation of the method the tests were later repeated on each subject after intravenous injection of morphine 1/6 gr. (11 mg.). This produced a definite rise in pain threshold, the analgesimeter readings rising from an average of 12 lb. to 24 lb. (5.4 to 10.8 kg.), and the response to the lightly mounted needle was much diminished, the sting alone being felt in one out of three pricks.

It appears, then, that in these doses *d*-tubocurarine chloride has no analgesic action, even at the height of muscular weakness.

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The campaign for wholesale immunization against diphtheria in Sweden was started in 1940, and in the period 1942-5 some two million doses were issued by the State bacteriological laboratory for this purpose. During the years between the two world wars, the incidence of diphtheria in Sweden was low, reaching a record low level in 1938 of only 107 cases. This comparative immunity has entailed a high and growing rate of non-immunes in the community, and in 1943 only 6.4% of 1,000 of Stockholm school-children were Schick-negative, but over 98% of school-children on receiving one dose became Schick-negative from being Schick-positive. Swedish practice now employs a single injection which, it is recognized, needs to be repeated after one and five years. The brevity of the immunity conferred by a single injection is emphasized by the observation that, a year and a half after a first injection, 57% of 600 children had in the interval again become Schick-positive while the remainder were still Schick-negative.

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