Trypsin in Duodenal Juice of Infants. Comparison of the Three Methods

Specimen No.	X-ray-film Method Spot No.	Gelatin Method (Andersen) Tube No.	Casein Method mg.N/ml.
1	Nil	Nil	Nil
2	"	"	"
3	2	9	4
4	6	4	52
5	6	3	67
6	7	4	67
7	7	2	85
8	7	2	96
9	7	2	115
10	7	2	124
11	8	4	54
12	8	3	83
13	8	3	88
14	10	4	93

all three methods (see Table). Although the results given for the x-ray-film method and Andersen's gelatin method show a close relationship, they are not exactly parallel. Of the three cases of fibrocystic disease, two showed no trypsin by both methods, and the third gave the same low result. However, among the normals, specimens of duodenal juice which gave identical levels of trypsin by the x-ray-film method gave levels that differed by as much as three tubes by Andersen's method. These differences are to be expected, since neither method can be considered accurate as compared with the casein method. For example, duodenal juice with an end-point at spot 7 can give a range of 67 to 124 mg. of nitrogen by the casein method and an even wider range is obtained with specimens of duodenal juice giving an end-point at spot 8. A similar wide variation is shown with Andersen's method. Results are, however, generally parallel with all three methods.

The results obtained in this investigation show that the x-ray-film method is entirely adequate for the differentiation of fibrocystic disease from other conditions. It is especially suitable as a routine clinical laboratory procedure; it is simple to perform, less juice is required, and it is less time-consuming than other methods, since results can be obtained within an hour. The use of James's method of intubation in conjunction with the x-ray-film method of estimation of proteolytic enzyme makes the investigation of suspected cases of fibrocystic disease of the pancreas relatively easy.

Summary

The amounts of trypsin in the duodenal juice of 48 infants and children, including 8 suffering from fibrocystic disease of the pancreas, have been determined by a method utilizing the gelatin of x-ray film as substrate. This method, which has advantages of ease and simplicity, has been compared with the gelatin method of Andersen as well as with a more accurate casein method, and has been shown to be accurate enough for the diagnosis of fibrocystic disease of the pancreas.

We would like to thank Dr. A. H. James for originally demonstrating his method of duodenal intubation, and Dr. W. F. Young and Dr. A. H. James for obtaining some of the specimens of duodenal juice.

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On the day of the total eclipse of the sun a million Hindu pilgrims bathed in the sacred lakes at Kurukshetra (East Punjab). *The Times* special correspondent (February 26) pays special tribute to the excellent public health arrangements. All pilgrims were inoculated compulsorily against cholera, all water (including the sacred lakes) chlorinated, and D.D.T. sprayed throughout the pilgrim camps, and no outbreak of disease has been reported.

ACUTE IDIOPATHIC PAROXYSMAL COLD HAEMOGLOBINURIA OF NON-SYPHILITIC TYPE IN A CHILD

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Haemoglobinuria, in contrast to haematuria, is a clinical sign which is so seldom seen in paediatric practice that its appearance is a matter of unusual interest and significance. In the great majority of cases there is either clinical or serological evidence of congenital or acquired syphilis, although in the last decade this disease has become increasingly rare.

The syndromes of paroxysmal cold haemoglobinuria associated with cold haemagglutination and paroxysmal cold haemoglobinuria as found in syphilitics were first clearly distinguished by Stats and Wasserman (1943). Cases of paroxysmal haemoglobinuria induced by exposure of the body to cold in which clinical and serological evidence of syphilis is lacking have been described by Stats and Wasserman (1943), Stats, Wasserman, and Rosenthal (1948), Malley and Hickey (1949), and Ferriman *et al.* (1951). These last observers, in an analysis of the reported cases, could find only 12 in which the aetiology is unknown. All were in the later age groups, only one (aged 38) being under 50.

Case Report

A boy aged 3½ was admitted to hospital with a history that on three days during the previous fortnight he had been out with his father (a general practitioner) on his rounds and, on returning home, complained of a headache and vague abdominal pain, had what appeared to be a rigor, and immediately afterwards passed dark urine "like burgundy." On each occasion very low environmental temperatures were present. His symptoms cleared completely in a matter of minutes and his urine became clear in about 12-18 hours. It had also been noticed that the child developed a dusky blue discoloration and puffiness of the hands and ears on exposure to cold, suggestive of Raynaud's phenomenon.

On admission the child was of normal size and weight, active, and of good nutrition. He was pale, with a slight icteric tinge. Neither liver nor spleen was palpable. His pulse was 70 and regular and the blood pressure 110/70. Pulsation of arteries in the upper and lower limbs was normal. There was no history of any previous illness. The family history was irrelevant.

Investigation of Urine.—During a paroxysm the urine was the colour of burgundy and of high specific gravity (1026-1030). Albumin was present. The benzidine test was positive and spectroscopy showed the presence of oxyhaemoglobin. No red cells were seen on microscopical examination. Immediately after an attack a trace of bilirubin was detected and urobilinogen was found in an increased amount. In the intervals between attacks spectroscopy did not show any oxyhaemoglobin and albumin was absent. Haemosiderin was present on two occasions only (Prussian-blue reaction).

Investigation of Blood.—During the period the child was under investigation the haemoglobin varied from 72% (10.7 g.%) to 82% (12.1 g.%) and the erythrocytes from 5.1 to 5.3 millions. Reticulocytes remained at 0.5%. The white cells varied from 8,000 to 13,000, with a normal differential count. The blood Wassermann reaction and Kahn test were repeatedly negative. The Donath-Landsteiner test was positive, serum haemolysins of the "cold" type being present to a titre of 1 in 4. An auto-agglutinin was present in the serum to a titre of 1 in 256 at 2–5° C. No agglutination occurred at 37° C. or at 20° C. (room temperature). When the tubes containing the "compatible" red cells which had been agglutinated by the patient's serum at 2–5° C. were warmed, complete and even dispersal of the cells occurred. No "incomplete" antibodies were detected, a direct Coombs test on the patient's red cells being negative. The acid haemolysis test (Ham, 1939) was negative. Oxyhaemoglobin and methaemalbumin (Schumm's test) were present in the serum during and shortly after an attack. The osmotic fragility of the red cells was normal.

Rosenbach Test.—While in hospital the child was encouraged to go outside lightly clad in the hope that a paroxysm might be induced; none occurred, probably owing to an improvement in the weather conditions. It was therefore decided to induce an attack artificially by a modified Rosenbach test in order to confirm the diagnosis.

Blood was taken from an arm; haemoglobin was not present in the serum, and urine passed at the same time contained no abnormal constituents. The same arm was immersed in water at about 5–10° C. for 10 minutes, no movement being allowed. Venous return was not obstructed. At the end of this period the arm was lifted from the bath. It was noted that the skin had become a mottled blue-and-white. Blood was immediately taken from the arm and a sample of urine obtained. The serum of this blood contained 380 mg. of haemoglobin per 100 ml.; methaemalbumin was present. The urine was of normal colour and contained haemosiderin, but no haemoglobin could be detected. The benzidine test was negative. Two hours later the blood serum still contained 250 mg. of haemoglobin per 100 ml. A specimen of urine obtained at this time was the colour of burgundy and contained haemoglobin and haemosiderin, the benzidine test being positive. No red blood cells were seen on microscopical examination.

Progress of Patient.—The child has been encouraged to lead a normal life and to go out in all weathers suitably clad—that is, wearing extra clothing, thick stockings, and gloves on exceptionally cold days. Eight months later no further attacks of haemoglobinuria had occurred, although occasional duskiness and puffiness of the hands in cold weather had been noticed. The child himself has not complained of any symptoms.

Discussion

In this country the only types of haemoglobinuria which need to be considered are (1) haemoglobinuria due to drugs, (2) march haemoglobinuria, (3) syphilitic haemoglobinuria, (4) paroxysmal nocturnal haemoglobinuria (the Marchiafava-Micheli syndrome), and (5) the idiopathic type.

The lack of any history of drug-taking or any preceding vigorous exercise clearly ruled out the question of drug or march haemoglobinuria. There was no past or present clinical or serological evidence of syphilis. The lack of persistent haemoglobinaemia and haemosiderinuria, the negative haemolysis test of Ham, together with the fact that the attacks occurred by day only, served to differentiate the condition from the Marchiafava-Micheli syndrome.

The diagnosis of haemoglobinuria due to cold agglutinins was finally confirmed by a provocative modified Rosenbach test and by the demonstration of autohaemagglutination at low temperatures and in high titre with complete reversal of the reaction upon increasing the temperature.

The child's paroxysms of haemoglobinuria, although dramatic and alarming events to the parents, appeared to cause little systemic upset. The degree of blood destruction

did not call for transfusion or even iron therapy. The adoption of common-sense precautions, such as the wearing of extra clothing on cold days, seems to have controlled the paroxysms without the necessity for curtailing the child's activities.

Summary

A case of idiopathic paroxysmal cold haemoglobinuria of the non-syphilitic type in a child aged 3½ is described. This is the youngest case yet reported.

The differential diagnosis of the types of haemoglobinuria met with in this country is discussed.

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INTRA-ARTICULAR STREPTOMYCIN IN TUBERCULOSIS OF THE KNEE

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Until recently the accepted treatment of synovial-joint tuberculosis was prolonged immobilization of the joint, general sanatorium treatment, and ultimately, in many cases, some form of arthrodesis. This leaves much to be desired, as the treatment lasts for years, a disability is nearly always permanent, and in children there is serious disturbance of growth.

With the advent of streptomycin many have attempted to modify the above regime, but with only a limited success. Most of the papers published (Bickel *et al.*, 1948; Smith and I-Sen Yu, 1950) have been of cases treated by systemic streptomycin in late and well-established infections. The tubercle bacillus is only moderately sensitive to streptomycin, so to obtain the best effect it is essential to procure the maximum concentration of the drug at the site of the lesion. This should be done early before extensive fibrosis and cartilage damage obliterates the joint space, damages the joint, and reduces the blood supply to the affected areas.

Early Diagnosis

To obtain these optimum conditions we have attempted to diagnose cases early by gland and/or synovial biopsy, and we have given streptomycin by the intra-articular route (Streeten, 1949).

By performing gland or synovial biopsies early in suspected cases a definite diagnosis can often be made (Arden and Scott, 1947). In the case of knee-, ankle-, wrist-, and elbow-joints a gland and/or synovial biopsy will give a positive result in 70–80% of cases. In the case of the hip- or shoulder-joint a synovial biopsy is hardly justified, but a gland biopsy can be readily carried out. We believe that all cases showing a chronic inflammatory process in a single large joint should be submitted to biopsy. Only by this method will it be possible to make an early diagnosis of a tuberculous infection of a joint.