(e) The various laboratory methods for detecting the function of the liver and bile can be either positive or negative in the presence of the hepatogenic syndrome, and they may or may not correspond to the clinical picture, which also may or may not be quite evident.

(f) In cases where the above laboratory tests are positive, they may become negative after ventrofixation.

(g) Where a retrodisplacement is associated with a hepatogenic syndrome clinically evident and proved by laboratory tests, mastopathy may often be present, the content of oestrogens is usually above normal, and endometrial biopsy mainly reveals metropathia. These conditions disappear in most cases after ventrofixation with no additional treatment.

(h) In our experience the incidence of retrodisplacement is very high among patients suffering from hepatocholecystopathy.

(i) The hepatogenic syndrome may or may not be associated with retrodisplacement, and vice versa; also, retrodisplacement, as known, does not necessarily always cause backache, lower abdominal pains, and menstrual disorders.

Conclusions

Retrodisplacement may very often cause the hepatogenic syndrome. Ventrofixation will in most cases cure the hepatogenic syndrome if this is due only to retrodisplacement. If retrodisplacement is not associated with the hepatogenic syndrome ventrofixation alone will either restore periods to normal or assist in the subsequent treatment with oestrogens.

Clinical symptoms are to our knowledge more demonstrative than laboratory tests, which, besides endometrial biopsy, cannot safely assist the diagnosis.

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What is the cost of living like in New York? The New York State Department of Labor, in its monthly news magazine, *Industrial Bulletin*, for March, 1952, explains how it makes an annual calculation of what a working girl needs to live, in order to fix minimum wages in eight industries which employ women. Weekly costs are given for September, 1951, and have risen a little since. They are quoted here in dollars, with the approximate English values, at \$2.80 equal to £1, in brackets afterwards. The average New York working woman needs a minimum of \$45 (£16) a week, of which \$6.3 (£2 5s.) goes at once in Federal and State income-tax. Housing, including fuel and light, accounts for \$4 and food for \$8 (£1 8s. 6d. and £2 17s. respectively), and she is allowed five lunches away from home a week at 68 cents (4s. 10d.) each. She must allow \$1.80 (12s. 10d.) a week for medical care; she spends \$6.9 (£2 9s. 2d.) a week on clothes, and will starve herself rather than spend less, and she has \$3.2 (£1 2s. 8d.) for leisure-time activities and amusements. The noteworthy things in this budget are the high rate of income tax, which takes 14% of her wage, and the enormous amounts spent on clothes and entertainment, which total over 22% of her earnings. The cost of medical care seems to be remarkably high, coming to something over £30 a year.

HAEMOGLOBINURIA IN A CASE OF CHOLERA

BY

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While studying the kidney changes and urinary abnormalities in cholera in order to evaluate the role of cortical ischaemia observed by some of us in experimental animals injected with cholera toxin (De, Sarkar, and Tribedi, 1950, 1951) and in human cholera (De and Sengupta, 1951), we stumbled on a sample of urine with typical port-wine colour. We became interested in the case and carried out certain laboratory investigations, which are recorded below along with the available clinical notes.

Case Report

A man aged 30 was admitted at 8 a.m. on March 4, 1952, with a history of frequent painless motions since 2 a.m. and one bout of vomiting. He had a dry tongue, a husky voice, severe dehydration, and an imperceptible pulse; his respirations were 26 a minute, and his rectal and axillary temperatures were 99° F. (37.2° C.) and 96° F. (35.6° C.), respectively.

The blood showed: haemoglobin, 70% (Sahli-Adams), or 9.9 g.%; red cells, 4,100,000 per c.mm.; white cells, 8,400 per c.mm.; no premature cell or malaria parasite; packed cell volume, 36%; mean corpuscular volume, 88 μ^3 , mean corpuscular diameter, 6.8 μ , mean corpuscular average thickness, 2.42 μ ; van den Bergh reaction of the serum, direct negative with indirect positive; total bilirubin, 1.17 mg. per 100 ml.; one-minute bilirubin, nil; plasma haemoglobin, 182 mg. per 100 ml. (measured with the help of photoelectric colorimeter); spectroscopic examination of plasma revealed absorption bands of oxyhaemoglobin (at 5,780 μ and 5,400 μ); osmotic fragility of erythrocytes, haemolysis started at 0.46%, was completed at 0.28% (Sanford technique); mean corpuscular fragility, 0.33%; effect of mechanical trauma, no lysis after 20 minutes' exposure of the washed red cells in a Kahn shaker (92 shakes a minute). The urine was first passed at 2 p.m.; port-wine colour; acid reaction, albumin +++; red blood cell +++++; hyaline cast +. The supernatant fraction of the freshly voided centrifuged sample showed absorption bands of methaemoglobin (at 6,300 μ , 5,780 μ , 5,400 μ , and 5,000 μ) and was positive to chemical test for blood. Stools had the appearance of rice-water; culture showed pure growth of Ogawa strain of *Vibrio cholerae*. The 8-hours and 72-hours broth culture of the strain were both non-haemolytic to human and sheep red cells.

Second Day.—The blood showed: haemoglobin, 74%, or 10.4 g.%; red cells, 4,780,000; reticulocytes, 0.9%; van den Bergh reaction, same as the first day; plasma bilirubin, 1.77 mg. per 100 ml.; plasma haemoglobin, nil; test for cold agglutinin, negative. The urine passed amounted to 528 ml. in 24 hours, with a specific gravity of 1016, and deep yellowish colour; acid reaction, albumin, +++; red blood cells, +++; granular casts, +; test for blood in the supernatant fraction of the centrifuged deposit was negative. Stools were five in number, liquid, and slightly coloured with bile.

The number and character of the stools improved from the next day. Haemoglobin percentage, plasma bilirubin, and urinary volume came down gradually, while the reticulocyte count never exceeded 1.04%. Albumin, red blood cells, and casts in the urine persisted throughout. The patient became restless and dyspnoeic with a blood non-protein nitrogen of 106 mg. per 100 ml. before he died on the tenth morning. Intravenous infusion of hypertonic saline was given on the first day and normal saline for the next two days. He was also given intravenous glucose, sodium bicarbonate, and vitamin C every day. Sulphaguanidine was continued up to the fourth day of illness.

After death the left kidney was removed by a lumbar incision because full necropsy was not permitted. The pathological findings will be communicated later along with those of other cholera kidneys. It may, however, be noted that there was no evidence of any pigment casts in the tubules.

Discussion

The presence of oxyhaemoglobin in heparinized plasma, or methaemoglobin in the supernatant fraction of the centrifugized urine, a high urobilinogen content of the urine, and a raised bilirubin content of the serum, together with direct negative and indirect positive van den Bergh reaction, provides ample evidence of the occurrence of considerable intravascular haemolysis in this case. The haemoglobin content of the plasma on the first day was 182 mg. per 100 ml., which was well above the renal threshold (135 mg. per 100 ml.) for haemoglobin (Gilligan *et al.*, 1941), and accounts for the leakage of haemoglobin, with consequent port-wine colour in the urine. It is significant that in our case no evidence of reticulocytosis was seen in spite of the preceding haemolytic process. Evidence of erythroblastic change in the bone marrow was not found by Chatterjee (1947) in cholera, and this may account for the absence of reticulocytosis. Acute anhydraemia, which prevails in cholera, is not by itself enough to depress erythroblastic activity as has been shown in rabbits by Cooray and De (1949). When all these points are taken into consideration, the role of absorbed cholera toxin in the inhibition of post-haemolytic reticulocyte response in this case becomes obvious.

The diagnosis of algid malaria followed by blackwater fever was considered. The isolation of agglutinable cholera vibrios from the typical stool left no doubt about the diagnosis of cholera, while absence of a history of febrile attacks, of residence in a hyperendemic area, of palpable spleen, and of parasites in the blood was thought to rule out blackwater fever. Besides, cold agglutinin, which has been demonstrated in cases of blackwater fever (Oliver-González, 1944; De, Sengupta, *et al.*, 1951), was not found in this instance.

Rogers (1921) observed slight haemolysis of the serum in some severe cases of cholera, but he recorded no haemoglobinuria. A high icterus index has been reported in cholera by Awny (1948), but no other evidence of haemolysis was noted. Manson-Bahr (1950) mentions jaundice as a complication of cholera, though the type and nature of the jaundice are not specified. These observations are suggestive of the presence of haemolysis in cholera, although its significance has not been stressed and the occurrence of haemoglobinuria is but a question of degree.

Acidosis and dehydration become the first suspect when investigating the cause of such a haemolytic process in cholera. Smith and Evans (1943) claimed that alteration of pH of the blood might be concerned in intravascular haemolysis. Harkins and Hastings (1931), however, recorded no evidence of haemolysis even when the pH of the blood was experimentally reduced to 6.12. Maegraith (1948) stressed the extremes of acidity necessary to disturb the buffering effect of the plasma sufficiently to alter the pH of the blood *in vivo* for any length of time. Liu *et al.* (1933) found the pH of the blood in cholera to be only 7.27 in the acute stage and 7.45 during convalescence. In

the light of the above observations such minor alteration in pH can hardly be held responsible for intravascular haemolysis in cholera. Regarding the role of dehydration, it has been clearly demonstrated by Cooray and De (1949) that acute severe anhydraemia maintained in rabbits for more than 10 hours does not in any way alter the morphology or fragility of the red cells, nor is there any evidence of liberation of haemoglobin in the plasma. In a corresponding manner no significant change in erythrocyte fragility or morphology could be detected in the present case to account for the observed haemolysis. Rogers (1921) attributed the haemolysis to hypochloraemia in cholera, but in his worst cases the plasma chloride was no less than 0.6%. In osmotic fragility tests for erythrocytes, haemolysis *in vitro* does not normally start above 0.46% sodium chloride solution. With the additional protective effect of the plasma *in vivo*, even 0.6% chloride cannot be regarded as low enough to bring about haemolysis of the cells. Reports of haemolysis following administration of sulphonamides to sensitive patients have been numerous (see Wintrobe, 1946). In the present case haemoglobinaemia and haemoglobinuria disappeared on the second day of the disease, while the sulphaguanidine was continued till the fourth day. The role of abnormal sensitivity to sulphonamide compounds can therefore be excluded in this case.

Lastly, one is left wondering if the cholera vibrios can be held responsible for bringing about the haemolytic process. A lot of work has been done in test-tubes, and bacteriologists have good reason to believe that true cholera vibrios are non-haemolytic. But in the light of more recent investigations such an opinion may have to be revised. Goyle's (1939) work indicates that the optimum time for demonstration of haemolysin may vary with different vibrios and different strains. A failure to detect haemolysis in the routine three-days culture cannot therefore rule out haemolytic activity of a vibrio. Several strains of true cholera vibrio have been found to produce haemolysin, which was demonstrable in eight hours' culture but which disappeared on 24 hours' incubation (Doorenbos, 1936a). Stone (1947) showed that an enzyme of *V. cholerae* rendered the red cells susceptible to lysis. Bernard and his co-workers (1939a) were able to extract a haemolysin from a five-days broth culture of true cholera vibrios. Bernard *et al.* (1939b) have advanced the hypothesis that one and the same haemolysin is common in both El Tor vibrios and true cholera vibrios, although their *in vivo* haemolytic activity may be different. Doorenbos (1936b) found a strain of *V. cholerae* whose haemolytic action was intermediate between the above two.

Manson-Bahr (1950) noted that El Tor strains may be true cholera vibrios contaminated with bacteriophage; the phage lyses the vibrios, liberating their content of endohaemolysin. More conclusive evidence in favour of the production of haemolysin by the true cholera vibrio has been adduced by Vassiliadis (1937), who has shown that it can give rise to an antihemolysin which completely neutralizes the haemolytic effect of the El Tor strains. The strain isolated from the present case apparently showed no haemolytic action *in vitro*, but, as noted above, this does not rule out its ability to produce haemolysin. Unfortunately, the stools of this case were not examined for evidence of any haemolysin which may be liberated by the disintegration of the cholera vibrios in the intestine. We are, however, collecting convincing evidence that samples of stool from other cholera cases showing pure growth of *V. cholerae* do contain a thermolabile agent which can lyse human red cells.

The present investigation leads one to suspect that cholera cases in general may be associated with variable degrees of intravascular haemolysis. Materials from further cases are being studied in this laboratory. The role of cholera toxin in the human disease has been debatable even to this day, and occurrence of haemolysis indicates that endohaemolysin, a bacterial product, is liberated and is absorbed into the

circulation, so that the clinical picture is not the simple effect of fluid loss. The question of haemolytic power of vibrios has so long remained an academic luxury of the laboratory man. It will now justify more fully the attention it has received, and will excite an equal if not a greater interest in the clinician.

Summary and Conclusion

The occurrence of haemoglobinuria, haemoglobin-aemia, and hyperbilirubinaemia is described in a case of cholera in which the patient died later of post-choleric uraemia. The strain isolated from the stool was a typical *Vibrio cholerae* (Ogawa type) with no evidence of haemolytic activity against sheep and human erythrocyte in either the 8-hours or the 72-hours culture. The possible roles of anhydraemia and acidosis, of alterations in the red blood corpuscles, and of sulphonamides in bringing about the intravascular haemolysis are discussed. It is suggested that endohaemolysin of *V. cholerae* is absorbed into the circulation and brings about the destruction of red blood cells.

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MASSIVE HAEMORRHAGE FROM THE ACUTE GASTRIC ULCER

BY

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In a proportion of cases of gastro-duodenal haemorrhage submitted to laparotomy no ulcer can be detected after a thorough external examination of the stomach and duodenum. Three courses are open to the surgeon; he can close the abdomen, he can open the stomach, or he can perform a wide gastric resection. Until recently I belonged to the first school of thought, believing that an invisible and impalpable ulcer was an acute lesion which might be expected to heal under conservative treatment. I was fortified in this belief by two cases in which the patients' recovery after simple laparotomy had been uneventful.

The following six cases, five of them occurring in rapid succession within a seven-weeks period, have

driven home the lessons that an acute ulcer can kill in spite of liberal transfusion, and that the lesion may be so small as to make its detection by a finger within the stomach extremely unlikely. These six patients had severe and repeated haemorrhages, but in all of them careful examination of the stomach and duodenum with the lesser sac widely open failed to reveal any outward evidence of active ulceration.

Case Reports

Case 1 (Simple Laparotomy).—Mrs. A., aged 75. History of indigestion for many years. Presenting symptom was haematemesis. Died six days after operation from repeated massive haematemesis, and in spite of the transfusion of 11 pints (6.3 litres) of blood. Necropsy revealed a shallow acute ulcer on the posterior wall of the body of the stomach.

Case 2 (Billroth I Gastrectomy).—Mrs. B., aged 76. History of indigestion for seven years. Presenting symptom was melaena, followed later by haematemesis. The resected specimen contained a shallow acute ulcer on the lesser curve of the stomach: the ulcer was irregular in shape, about the area of a sixpence, and there was a small vessel, plugged with recent clot, in its base. The scar of a healed ulcer was visible on the posterior wall of the stomach. Her post-operative condition was good for three days, after which it rapidly deteriorated, and she died from peritonitis on the fifth day. The necropsy had certain features of interest, and the findings are discussed below.

Case 3 (Polya-Hofmeister Gastrectomy).—Mr. C., aged 71. No history of previous indigestion. Presenting symptom was melaena, followed later by haematemesis. The resected specimen contained a shallow ulcer high on the lesser curve. No open vessel could be seen and the ulcer was little more than an erosion. This patient had repeated severe melaena, and received 13 pints (7.4 litres) of stored blood in four days. Whilst awaiting his anaesthetic in the theatre he had a massive haematemesis of about 2 pints (1.14 litres), followed by a convulsion and profound collapse. He was revived by artificial respiration and forced transfusion by the anaesthetist (Dr. J. Rochford), and the operation was begun as soon as the systolic pressure reached 90. It is clear that this patient was bleeding furiously from an acute ulcer, and that his only hope lay in urgent surgery. He made an excellent recovery, but his convalescence was somewhat delayed by threatened disruption of the abdominal wound. This complication was averted by conservative treatment with strapping.

Case 4 (Polya-Hofmeister Gastrectomy).—Mrs. D., aged 50. Two years' history of indigestion, the last attack starting three days before admission. Presenting symptom was melaena, followed later by haematemesis. The resected specimen contained a shallow acute ulcer with an open vessel in its base. This patient had two attacks very suggestive of pulmonary embolism on her sixth post-operative day. She was treated with intravenous heparin, and her subsequent recovery was uneventful.

Case 5 (Polya-Hofmeister Gastrectomy).—Miss E., aged 58. History of three months' indigestion, last attack starting 24 hours before admission. Presenting symptom was haematemesis. The specimen contained a shallow acute ulcer with an open vessel in its base. Convalescence was uneventful, except for an infected haematoma of the abdominal wound.

Case 6 (Polya-Hofmeister Gastrectomy).—Mr. F., aged 50. History of two years' indigestion, last attack starting two weeks before admission. Presenting symptom was melaena, followed later by haematemesis. The specimen contained part of an acute ulcer high on the lesser curve; the remainder of the ulcer had been crushed by a clamp and was included in the Hofmeister valve. Recovery was uneventful.

Four of these six patients were admitted under the medical care of Dr. G. Riddell Royston, and the other two (Cases 4 and 5) were admitted under Dr. Bruce Williamson. Cases