In the literature very little was to be found about the comparison between the oral and intravenous methods. A comparative study by B. Ottenstein (unpublished) of both methods of application in normal and luetic patients convinced us that the intravenous method is slightly more sensitive than the oral one.

The tests were made in the morning between 9 and 12 o'clock. The patients, who had had a light breakfast at home, were injected slowly with a freshly prepared solution of 1.77 g. of sodium benzoate in 20 c.cm. of distilled water. The injection took not less than 4 to 5 minutes. Most of the patients showed no reaction at all, some a little dizziness during the injection. They were advised to urinate before the injection and then rested for exactly one hour, after which the urine was used for the estimation. Amounts of urine of less than 100 c.cm. were immediately acidified with 25% hydrochloric acid to Congo-red reaction (about 1 c.cm.) and vigorously stirred with a glass rod until precipitation of hippuric acid crystals started. These were allowed to stand for at least one hour in the ice-box. The supernatant fluid was then filtered off with a suction pump and the crystals repeatedly washed with a little cold water until the original container was entirely clean. The filter paper was carefully removed from the funnel and the crystals washed into a small beaker with a little hot water. The crystals were then dissolved by heating and immediately titrated with N/5 sodium hydroxide against phenolphthalein. Calculations were done according to the original prescription by Quick (1936), and the results expressed as milligrammes of benzoic acid. If the excreted urine was more than 100 c.cm. it was first slightly solidified with acetic acid and concentrated to about 50 to 70 c.cm. on a boiling-water bath. The estimation was then made as described above.

Results

Control Group (20 women, non-pregnant).—Mean average, 0.768; range, 0.41–1.10; standard deviation, 0.22; standard error, ± 0.05 ; coefficient of variation, 29.1%.

Pregnant Women (50 cases).—Mean average, 0.43; range, 0.15–0.76; standard deviation, 0.16; standard error, ± 0.02 ; coefficient of variation, 37.2%.

Discussion

The findings of Neuweiler (1939) were fully confirmed. In late pregnancy there was a marked decrease in the excretion of hippuric acid after intravenous injection of sodium benzoate. In our series only one of the pregnant women reached the level of the mean average of the control group. On the other hand, four of the 20 controls showed a rather low output and two more showed a value slightly under 0.7. This figure is generally accepted as the lower limit of normal. These patients had no symptoms which could explain the low values. Therefore, as some non-pregnant women show a decrease in hippuric acid excretion and some pregnant women have only a slight diminution of the normal excretion, one has to be cautious in drawing conclusions. One has to consider whether the doubtlessly existing lowering of the hippuric acid excretion might be only the expression of a physiological peculiarity of the state of pregnancy. According to Quick (1931), the benzoic acid is conjugated in the liver with glycine, thus forming hippuric acid, which is excreted by the kidneys. If no food rich in glycine is taken previously the glycine is synthesized in the liver at a constant rate roughly proportional to the surface area of the patient, provided the ingested dose of benzoic acid is big enough. Since the excretion of hippuric acid by the kidneys is even faster than its synthesis (Quick, 1931), a low rate of excretion after administration of benzoic acid in the almost fasting state is a measure of the ability of the liver to synthesize glycine. But as in kidney impairment there is a retardation in the excretion rate of formed hippuric acid (Snapper and Grünbaum (1924) have found an increase in hippuric acid in the blood after administration of benzoic acid in cases of renal sclerosis), this possibility has also to be considered, since retention of nitrogen during pregnancy is quite common. The intake of benzoic acid and glycine in a fairly large amount would clarify this question. Investigations on this line are in progress.

Considering theoretically all possible explanations of our findings in view of the peculiarity of the state of pregnancy, there remains another problem to be discussed. Again according to Quick, together with the conjugation of benzoic acid

with glycine there is also a conjugation with glucuronic acid, which forms glucuronic acid–monobenzoate. The portion of benzoic acid appearing in the urine combined with glucuronic acid is generally insignificant, owing to the fact that when glucuronic acid–monobenzoate is administered it is eliminated as hippuric acid and the glucuronic acid presumably becomes oxidized. With regard to the occurrence of glucuronic acid in pregnancy very little is known; but we do know that of the total amount of oestradiol in pregnancy a high proportion is converted to the inactive oestriol, and this, at least to a certain degree, is combined with glucuronic acid. It might be hypothetically assumed that there is a greater need of glucuronic acid in the body during pregnancy, and this fact may interfere with the usual conjugation of benzoic acid and glycine. This problem, too, will be investigated and reported on later.

Conclusion

The excretion of hippuric acid has been tested after intake of 1.77 g. of sodium benzoate intravenously in 50 women during the last trimester of pregnancy; 20 non-pregnant women acted as controls.

Most of the pregnant women showed a marked decrease in hippuric acid excretion: an explanation of this phenomenon has been discussed.

The generally low output of hippuric acid after intake of sodium benzoate in pregnancy makes this test inapplicable where hepatic diseases are associated with that condition.

We wish to express our gratitude to Prof. Nasid Erez, director of the clinic, for having given all facilities for making this investigation.

REFERENCES

- Higgins, G., O'Brien, J. R. P., Stewart, Alice, and Witts, L. J. (1944). *British Medical Journal*, **1**, 211.
Neuweiler, W. (1939). *Klin. Wschr.*, **18**, 1050.
Quick, A. J. (1931). *J. biol. Chem.*, **92**, 65.
— (1936). *Arch. intern. Med.*, **57**, 544.
— Ottenstein, H. M., and Weltchek, H. (1938). *Proc. Soc. exp. Biol.*, N.Y., **38**, 77.
Rennie, J. B. (1942). *Brit. J. exp. Path.*, **23**, 329.
Snapper, J., and Grünbaum, A. (1924). *Klin. Wschr.*, **3**, 101.

SULPHAPYRIDINE ANURIA IN GURKHAS

BY

C. W. HEALEY, M.C., M.D.

Lieut.-Col., R.A.M.C.; Hon. Asst. Physician, N. Staffs R.I.

(From a Military Hospital in India Command)

From November, 1944, to February, 1945, five cases of sulphapyridine anuria in Gurkhas were admitted to this hospital. Two were treated medically and three surgically. All terminated favourably. Perhaps the most interesting one was the following.

Case History

The patient, a Gurkha soldier aged 18, was admitted to another hospital with bronchopneumonia on Jan. 12, 1945, and was treated with sulphapyridine, 1 g. four-hourly, along with vitamin C tablets. Next day he was transferred to a second hospital, where treatment was modified to 1 g. of sulphapyridine every six hours. This treatment was continued during the 14th and 15th, when his general condition showed a marked improvement and chest examination revealed only rhonchi scattered throughout the lungs.

At 6 a.m. on Jan. 16 the patient, whose output of urine was diminishing so that fluids were pressed, complained of severe pain in the epigastrium and painful micturition. The sulphapyridine was stopped immediately, after 23 g. had been given, and the patient received the usual medical treatment for sulphonamide anuria. Later that day he was transferred to this hospital, 25 miles away. He had last passed urine (4 oz.: 114 c.cm.) about midnight on Jan. 15/16.

On arrival at 9 p.m. on Jan. 16 the patient was complaining of frequent vomiting and of severe cramp-like epigastric pains. He thought that during the journey he had passed a few drops of urine with much straining. He was, drowsy and slightly cyanotic. T. 97.4° F. (axilla); P. 120, rhythmic, equal, full; R. 36; B.P. 115/85. Pupils were miotic and reacted sluggishly to light; tongue dry and furred; ankle- and knee-jerks brisk; cryaesthesia. Examination of the lungs did not reveal any area of consolidation, but only generalized rhonchi and gross rales.

He was examined and his bladder washed out with luke-warm sodium bicarbonate solution. Medical treatment was continued, with

plenty of fluids and alkalis by mouth and hot applications in both kidney regions. With his vomiting the patient ejected three round-worms. At 2 a.m. on the 17th he passed with difficulty a few drops of smoky urine. He was also given a continuous intravenous drip of glucose-saline. At 8.30 a.m., after a little sleep, he felt more comfortable. His intake of fluid in this hospital so far had been 48 oz. (1.1 l.), but no urine other than the few drops already mentioned had been passed. His condition was stationary except that he was rather drowsier than before. T. 96.2° F.; P. 70, hard, full; R. 36; B.P. 145/100; blood urea 48 mg. per 100 c.cm. Condition of the chest unchanged. Medical treatment was continued all day and the bladder was washed out twice without result. At 5 p.m., in view of the persistent anuria and the progressive increase of the uraemic symptoms, operative treatment was decided upon. A venesection of 300 c.cm. was done, followed by an intravenous drip transfusion of glucose-saline. At 6.15 p.m. the patient was given an injection of morphine. At 7 p.m.—43 hours after the anuria had begun—right-sided nephrotomy was carried out under local analgesia.

At operation the kidney was found enlarged and congested, and showed small localized subcapsular swellings containing urine; an incision from the convex border to the pelvis was made for a length of about 1½ in. (4 cm.) and a rubber catheter stitched in. Lavage of the pelvis with a solution of sodium bicarbonate was carried out, followed by lavage of the bladder with the same solution. There was no occlusion of the ureter. After the operation the patient was given a subcutaneous saline injection of 400 c.cm. and alkalis by mouth at regular intervals. He spent a good night; I oz. (28.4 c.cm.) of urine was collected through the catheter, and the bedding was found to be soiled with urine the next morning. He looked better and vomiting had stopped. T. 100.2° F.; P. 70; R. 22. At about 12 noon his temperature went up and the clinical examination showed consolidation of the right lower lobe of pneumonic type. Fever of the high remittent type continued on Jan. 19 and 20 (see Chart). During this period the patient passed an increasing quantity of urine by the catheter and per urethram. He looked very ill, cyanosed, and dyspnoeic, so symptomatic treatment was given. The blood urea on Jan. 19 was 55 mg. per 100 c.cm.

At 4 p.m. on Jan. 18 sodium penicillin treatment had been started, 15,000 Oxford units every three hours (concentration 5,000 units per c.cm.; the potency having been checked by the station laboratory). In the morning of the fourth day of treatment (Jan. 21) the patient looked better, although his local condition remained unchanged and he was found to have developed a bed-sore. His temperature was down for the first time after the operation, but in the evening it went up again. Clinical examination showed, besides the pneumonia of the right lower lobe, the presence of scattered patches of bronchopneumonia in the right upper and left lower lobes. At about 4 p.m. the patient developed a crisis of asphyxia, with tracheal rales, which was overcome only by continuous inhalation of oxygen, digitaline, and camphor in oil.

At that time (the catheter had been removed the day before) the patient was passing a fair quantity of strongly alkaline urine; his W.B.C. count was 8,100 and his blood urea 32 mg. per 100 c.cm. In view of impending disaster, the chance was taken of giving him 1 g. of sulphadiazine four-hourly. He had his first dose at 5 p.m., and the next morning seemed somewhat improved. The course of the temperature is shown in the Chart. Sulphadiazine was con-

tinued in doses of 1 g. eight-hourly until Feb. 1, when it was cut down to 0.5 g. eight-hourly (W.B.C., 5,900) and the next day discontinued altogether. As adjuvant therapy he was given 2 c.cm. of nikethamide twice daily. His blood urea on Jan. 31 was 22 mg. per 100 c.cm.

The recovery of the patient was quick and satisfactory, and on March 4 he was discharged from hospital.

Comment

Assuming that the normal precautions taken in sulphonamide therapy were observed (as they appear to have been) before the patient's admission to this hospital there seem to be two possibilities: (a) that the sulphapyridine used had become toxic; and (b) that Gurkhas, having never experienced Western medication, are particularly liable to fail to excrete the products of modern chemotherapy. As, however, the same consignment of sulphapyridine has been used in several hundreds of cases

of British and Italian patients without any untoward results, the former explanation is considered unlikely.

In all cases burning micturition, shortly preceding the oliguria, was the first symptom. Cystoscopic examination revealed great haemorrhagic suffusion and congestion of the mucosa of the bladder, obviously making any attempt at ureteral catheterization difficult and dangerous. No signs of tubular obstruction were seen at any of the operations. The absence of these—which one would expect to be present if the acetyl-sulphapyridine is to reach such a concentration in the urine as to be precipitated in the lower third of the ureter and uretero-vesical orifice—and the free passage of the bicarbonate solution which was introduced into the pelvis of the kidney to the bladder, rule out any possibility of mechanical obstruction of the renal tract as the cause of the anuria in the three cases. At no time has any crystal of a sulphonamide derivative been seen either at operation or in the urine, even microscopically.

The operation revealed in all three cases a kidney with no signs of hydronephrosis of the pelvis but small subcapsular sacs containing urine. The kidney, especially the medulla, was found congested. We believe that this condition of congestion—a toxic nephrosis—of the kidney may be the primary cause of the anuria.

The blood urea, which has been found to approximate closely in Gurkhas to the normal European standard, rises rapidly, especially in the second 24 hours after anuria has become established, reaching not far from 60–80 mg. per 100 c.cm. after 24 hours. We consider it advisable to try medical treatment for the first 24 hours after the onset of burning micturition and oliguria, and to resort to surgical measures if such treatment meets with no success.

It is regretted that owing to Service conditions no bibliography is available.

I should like to express my thanks to the various members of the hospital staff, Indian and Italian, and especially Cap. Del Rio M., of the Corpo Sanitario Italiano, and Major B. L. Raina, I.A.M.C., for their excellent work and loyal co-operation; also to Col. K. S. Master, M.C., K.H.P., for his kind interest and permission to publish this note.

ACUTE PANCREATITIS

BY

NORMAN G. GODFREY, F.R.C.S.

Surgical Specialist (Full-time, Temporary), Crumpsall Hospital, Manchester

Acute pancreatitis is one of those conditions concerning which it is difficult to formulate definite ideas as to diagnosis and treatment, for the disease varies enormously in its severity, and statistics as to the mortality rate under different forms of treatment are often misleading. This article is written in an endeavour to clarify some points concerning its diagnosis and treatment.

Before considering the diagnosis it is necessary to stress several facts which are well known.

(1) The disease varies from an extremely severe catastrophic condition to a mild abdominal upset, which in the majority of cases is not recognized as a pancreatitis.

(2) A definite clinical diagnosis is extremely difficult. In a study of recent literature on acute pancreatitis the following figures are of significance. Pre-operative diagnosis: All cases were operated upon at varying intervals from the time of onset of symptoms. In those operated on under 72 hours from onset the pre-operative diagnosis was incorrect in a much higher proportion of cases:

Pre-operative diagnosis:	Cases
Acute cholecystitis	26
Acute pancreatitis	20
Perforated peptic ulcer	8
Acute appendicitis	3

Criteria for a Diagnosis of Acute Pancreatitis.—In considering the diagnosis of acute pancreatitis in a series of cases it is necessary to have some criteria on which the diagnosis is based. In this series, and in the cases taken from the literature, the diagnosis has been made on one or more of the following: (1) evidence of acute pancreatitis seen at necropsy; (2) evidence of acute pancreatitis seen at operation; (3) clinical evidence associated with a urinary diastase above 50 units. Any cases which clinically may have been acute pancreatitis but did not fulfil one or more of the above conditions have been excluded from this discussion.