thirds of the way across the muscle. More length is seldom required laterally unless it is desired for mobilizing the duodenum. It can be obtained by splitting the external and internal oblique and the transversalis muscles in the direction of their fibres. This incision over the gall-bladder gives an excellent exposure of the biliary passages and it is

FIG. 2.—The incision completed.

easy to explore the common bile duct and, in the average case, to pass the standard Desjardins forceps down this duct. For a barrel-chested patient with a high liver I have a more curved pair of Desjardins forceps available. Should more room be required medially the incision is extended through the linea alba into the left rectus sheath. As the incision lies between the eighth and ninth intercostal nerves, these nerves are in no danger of injury and do not have to be identified (Fig. 1). Should the lateral margin of the incision be made a little low the ninth intercostal nerve is seen lying on the posterior layer of the rectus sheath near its lateral margin. The direction of the ninth nerve at this point is that taken by the ninth rib in the axilla (Fig. 1).

Anatomical Points

Identification of Ninth and Tenth Costal Cartilages

The tenth costal cartilage can be felt by running the finger outwards along the smoothly curving lower costal margin till a definite step is felt, which is caused by the tenth costal cartilage. Fig. 1 shows the usual way the tenth cartilage turns up to form this step. In two cases the tenth rib was floating and did not articulate with the ninth, reminiscent of the three floating ribs of the anthropoids. The narrow spear-like tip of the ninth costal cartilage can be felt only by taking the ninth costal cartilage between the right finger and thumb, where it is lying along the postero-inferior border of the costal margin, and, by moving it, to feel with the other hand its sharp tip where it articulates with the broad eighth costal cartilage. This identification of the tip of the ninth is not a necessary step of the operation, but it is of interest in the diagnosis of gall-bladder tenderness, which is situated most commonly 1 in. (2.5 cm.) below the tip of the ninth costal cartilage on a line drawn from the tip of that cartilage to the umbilicus. It is the surface marking of the infundibulum (Hartmann's pouch), where, with the patient supine, stones tend to gravitate.

Direction of Fibres in Rectus Sheath

On exposing the anterior layer of the rectus sheath, fibres of the external oblique are seen running downwards and

FIG. 3.—Showing fusion of the external oblique aponeurosis with the internal oblique.

medially across the line of the incision. If, however, the anterior rectus sheath is inspected on its deep side the fibres of the internal oblique are running upwards and medially along

The posterior layer of the rectus sheath shows the stout fibres of the internal oblique running upwards and inwards along the line of the incision. The red muscular fibres of the transversus abdominis show through the outer third of the posterior layer of the sheath. These muscular fibres run transversely as a thin aponeurotic layer which becomes fused with the posterior rectus sheath at the junction of the outer and middle thirds of the sheath. The transversus aponeurotic fibres are by far the weaker component of the posterior rectus sheath.

Course of the Intercostal Nerves

The ninth intercostal nerve leaves the subcostal groove about the mid-axillary line and runs downwards and forwards, passing behind the tenth costal cartilage where the cartilage is turning up (Fig. 1). It lies on the transversus muscle and is below the line of the incision. The eighth intercostal nerve as it passes behind the ninth costal cartilage is directed upwards and medially and is above the line of the incision. In dividing the rectus muscle a fine twig connecting the eighth and ninth nerves can occasionally be seen. The line of incision runs between these nerves (Fig. 1).

Anatomical dissections by Davies, Gladstone, and Stibbe (1932) have shown that the rectus muscle does not receive a segmental supply from one intercostal nerve. As a result of communications in the thorax, and again between intercostal nerves when lying on the transversus abdominis muscle, any one segment of the rectus is supplied by at least three intercostal nerves. The division of any minor connecting branch in the rectus muscle does not affect the strength of the rectus muscle when the incision is healed.

I wish to thank Sir Wilfrid Le Gros Clark for drawing my attention to the work of Davies, Gladstone, and Stibbe and to the skeleton of the anthropoid, and to Miss M. C. McLarty for the drawings.

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MULTIPLE TOXIC EFFECTS OF PHENYLBUTAZONE

REPORT OF A FATAL CASE

BY

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It is almost four years since Currie (1951) first drew attention to the therapeutic effect of phenylbutazone ("butazolidin"). Since then it has been employed extensively both in hospital and in general practice, and many reports on its use, mainly in the treatment of rheumatoid arthritis, have appeared in the medical press. There is general agreement that the drug has a marked analgesic action in rheumatoid arthritis in roughly one case in three, but it is doubtful whether it has any anti-inflammatory properties. As Hart (1953) pointed out, although occasionally a reduction of inflammatory swelling is seen, increase in range of movement and function tests, and decrease in stiffness, are essentially secondary to the relief of pain. Steinbrocker (1953) reported on the results he had obtained in a large series of patients on short- and long-term phenylbutazone treatment, and came to the conclusion that the drug was a powerful analgesic but that its antirheumatic effect, if any, was slight.

Since the introduction of phenylbutazone in the treatment of the rheumatic diseases numerous reports of its

toxic effects have been published, the incidence varying between 20 and 50%. While the majority of the side-effects are of a mild nature, serious complications have been encountered from time to time, and a not insignificant number of fatalities have been attributed to the use of this drug. Deaths due to agranulocytosis (*British Medical Journal*, 1952; *Lancet*, 1953; Newns, 1953; Etes and Jacobson, 1953; Steinberg *et al.*, 1953; Dilling, 1953; Wood, 1954), aplastic anaemia (Leonard, 1953), haematemesis (*British Medical Journal*, 1952), perforation of a peptic ulcer (Benstead, 1953), and to renal failure (Bruck *et al.*, 1954; Johnson and Larkin, 1954) have been recorded. The non-fatal complications are by now well known, and include sodium retention with oedema, various types of skin rashes, activation or perforation of a peptic ulcer, agranulocytosis, thrombocytopenia, nausea, vomiting and diarrhoea, jaundice, and bleeding manifestations with resultant anaemia—for example, haematemesis, melaena, and haematuria. Many patients have experienced two or more complications at the same time (Hart, 1953; Pemberton, 1954). The following case, which had a fatal termination, is of interest in that multiple toxic reactions, including a polyneuritis, made their appearance during the administration of phenylbutazone.

Case History

A single woman aged 41 was admitted to hospital on July 3, 1953, with a history of rheumatoid arthritis of seven years' duration, involving her hands, wrists, ankles, and feet. Six months before admission her doctor put her on phenylbutazone, when she was given 600 mg. a day for one week, 500 mg. a day for two days, and then 400 mg. for one day. The drug had to be discontinued at this point on account of a haematemesis of moderate severity. This was accompanied by ulceration of the mouth and lips. Recovery from the haemorrhage was rapid and the buccal ulcers healed. Six weeks later her joints became so painful that she persuaded her doctor, against his better judgment, to let her resume the phenylbutazone. She was put on 200 mg. daily, and this gave her considerable relief from pain. She was maintained on this dose for three months, when a rash appeared on her legs and the drug was stopped. After a few days the ulcers reappeared in her mouth and mild jaundice was noted by her doctor. Two weeks later she developed weakness of her arms and legs, and within a week she was unable to move her arms or legs. This was unaccompanied by pain.

On admission she was seen to be a thin and ill-looking woman with a sallow complexion, and lay limply in bed. She was afebrile, with a mild tachycardia. There was no evidence of jaundice. Multiple small punched-out ulcers were present on the ankles and feet, and a few superficial ulcers were seen on the lips and in the mouth. There was loss of all types of sensation in the arms below the elbows and in the legs below the knees. Weakness of the shoulder-girdle and hip muscles and complete loss of power below the elbows and knees were present. All deep reflexes in the arms and legs were absent; the plantar responses were flexor. There were chronic rheumatoid changes in the fingers, wrists, knees, ankles, and feet. The liver and spleen were not palpable. The heart and lungs were normal.

Laboratory investigations on admission resulted as follows: haemoglobin, 65%; red blood cells, 3,750,000; white blood cells, 11,800; blood film, normal; erythrocyte sedimentation rate (Westergren), 96 mm. in one hour; blood W.R., negative; blood urea, 30 mg. per 100 ml.; blood uric acid, 1.9 mg. per 100 ml.; plasma proteins, normal; thymol turbidity, 3 units; thymol flocculation, positive after 4 hours; alkaline phosphatase, 3.5 K.A. units per 100 ml.; van den Bergh, negative; icterus index, 4; urine: no sugar, albumin, bile, or urobilin; faecal occult blood, positive.

In spite of intensive medical measures, physiotherapy, and splintage, her condition slowly deteriorated and she became emaciated. Flexion contracture of the fingers and subluxation of the knees developed. She was unconscious for three days before she died on January 28, 1954, seven months from the date of admission.

Necropsy.—The body was that of an extremely emaciated woman with numerous pressure sores over the bony prominences. A moderate degree of rheumatoid arthritis of the fingers, wrists, knees, and ankles was noted. The heart appeared normal. The lungs showed evidence of a bilateral bronchopneumonia with abscess formation. Abdomen: a lesser-curvature posterior-wall chronic ulcer, 12 by 7 mm., with a small perforation and associated peritonitis, was found; the liver weighed 1,140 g. and was soft and pale; a few small gall-stones were present in the gall-bladder, which was small and had a thickened wall; the spleen was congested; the genito-urinary organs were normal. Endocrine glands: the pituitary, thyroid, and adrenals were normal. Apart from some general pallor and oedema, the brain was normal. Macroscopically, no gross abnormality was seen in the spinal cord or peripheral nerves.

Histological Examination.—There was evidence of a widespread polyneuritis with marked degeneration and vacuolation of the posterior columns of the cord. Both median nerves showed almost complete loss of myelin sheaths and very severe loss of axis cylinders. The ulnar nerves presented a similar but slightly less marked appearance. Many nerve bundles in the sciatic nerves looked shrunken, and the myelin sheaths stained irregularly, but the axis cylinders were well preserved. The liver showed a moderate degree of fatty infiltration around the portal tracts. There was no evidence of central necrosis. The spleen was normal. Some focal cellular infiltrate and tubular atrophy, with an occasional damaged glomerulus, were seen in the kidneys. A bronchopneumonia with abscess formation was present in both lungs.

Discussion

This case presents some interesting features. The patient received a total of only 5.6 g. of phenylbutazone prior to the haematemesis, which was of moderate severity. Careful questioning did not reveal any previous history of gastric disturbance. In addition to the haemorrhage, superficial ulceration of the mouth and lips was noted, a finding which may well have reflected the state of the gastric mucosa at that time. Multiple superficial gastric erosions were reported at necropsy by Dilling (1953) in a case of fatal agranulocytosis following phenylbutazone therapy.

It is obvious that treatment with phenylbutazone should have been permanently discontinued at this point, but six weeks later it was resumed at the patient's own request, and she was maintained on it for a further three months, when the second series of side-effects made their appearance.

It will be seen that this patient had six complications in all. Four of these—namely, ulceration of the mouth, rash, haematemesis, and perforation—could be directly attributed to the administration of phenylbutazone, as all are now accepted as toxic effects of the drug and have been reported on frequent occasions. Whether the jaundice and polyneuritis were associated with the use of the drug is difficult to establish, for as Currie *et al.* (1953) pointed out, not all symptoms occurring during drug therapy are necessarily due to the drug. While jaundice, mainly of the obstructive variety, has been reported from time to time (Bourne, 1953; Solomon, 1953), post-mortem examination in this case revealed several small calculi in the gall-bladder and only some fatty infiltration of the liver. The icterus, therefore, could have been due either to obstruction of the common bile duct by a gall-stone or to a mild toxic hepatitis, followed by regeneration of liver tissue.

Headache and vertigo have occasionally been encountered during phenylbutazone therapy, but neurological signs are apparently rare. Loxton *et al.* (1952) reported a case which developed a lesion of the central nervous system with

paralysis of the left leg and urinary incontinence and which they attributed to a haemorrhagic transverse myelitis. While the evidence incriminating phenylbutazone as the cause of the polyneuritis in the present case is purely circumstantial, no other aetiological factor could be demonstrated.

The immediate cause of death was presumably the acute peritonitis resulting from perforation of the gastric ulcer in an emaciated and moribund subject. Clearly, a fatal issue could, and should, have been avoided if the phenylbutazone therapy had been permanently discontinued by her doctor at the time of the haematemesis. It demonstrates once more how vital it is that medical men should not be influenced in their judgment by the entreaties of the patient.

It is generally accepted that phenylbutazone is rapidly absorbed when given by mouth. Pemberton (1954) regarded a blood concentration of 12–16 mg. per 100 ml. as the therapeutic range of the drug. On the other hand, Currie *et al.* (1953) found that an initial blood concentration of 8–11 mg. per 100 ml. was sufficient to suppress the symptoms, and that remission could be maintained by much lower concentrations—4.6 to 8 mg. per 100 ml. Bruck *et al.* (1954) obtained maximal suppression of symptoms in their series at any level between 5 and 10 mg. per 100 ml. Phenylbutazone is slowly eliminated from the body (Burns *et al.*, 1952), and appreciable levels remain in the blood for at least two weeks after the cessation of treatment (Pemberton, 1954). Toxic effects, therefore, can be expected after the drug has been withdrawn. Shields *et al.* (1953) reported a case in which perforation of a gastric ulcer occurred seventy-two hours after discontinuation of phenylbutazone therapy, and Wood (1954) a case in which a rash appeared six days after the drug was stopped.

Some observers (Bruck *et al.*, 1954) have found a striking correlation between the frequency of toxic reactions and the blood phenylbutazone level, while others (Leonard, 1953; Nassim and Pilkington, 1953; Pemberton, 1954) have failed to confirm this observation, and feel that the administration of small doses of phenylbutazone does not eliminate the possibility of the occurrence of toxic side-effects. In the case reported here a moderately severe haematemesis with ulceration of the mouth and lips developed after a total dosage of only 5.6 g., the maximum dose being 600 mg. a day. This raises the question whether the toxic effects of phenylbutazone are due entirely to over-dosage or whether an idiosyncrasy to the drug may be responsible in certain cases. Support for the latter view has been produced by O'Brien and Storey (1954), who recorded a case in which they attributed the cause of death during phenylbutazone therapy to a hypersensitivity reaction, which was manifest histologically by three types of lesion: polyarteritis nodosa, hypersensitivity angitis, and granulomatous lesions. A severe case of sensitivity to phenylbutazone with the features of Stevens-Johnson syndrome and granulocytopenia was described by Steel and Moffatt (1954). It has also been suggested that agranulocytosis may be due to an idiosyncrasy to the drug (Stifel and Burnheimer, 1953), and that the drop in the white-cell count is sudden, so that daily counts, which give a false sense of security, are of doubtful value in anticipating this complication.

If toxic symptoms develop during phenylbutazone therapy the drug is generally withdrawn either temporarily or permanently, according to the nature and severity of the reaction. Many observers advocate the resumption of the drug, usually on a smaller dosage, once all signs of the reaction have disappeared, except in cases with the more serious complications. In this connexion, Fishman and Reynolds (1953) issued a warning, stating that it was unwise to resume treatment with phenylbutazone, however mild the toxic effects. They reported the case of a woman who received phenylbutazone for a whiplash injury of the neck following a car accident. A mild rash appeared after she had taken sixteen 200-mg. tablets, and was of the morbilliform type. This began to subside fairly quickly with treat-

ment and omission of the drug, and had almost disappeared when, for no obvious reason, it suddenly flared up again and developed into an exfoliative dermatitis which nearly proved fatal.

My experience with the present case, added to an overall incidence of 26% of toxic reactions, including four patients with severe haematemeses, forces me to the conclusion that phenylbutazone is a dangerous drug and that the risks attached to its use in rheumatoid arthritis are not outweighed by its advantages. As it is still widely employed in general practice, where for obvious reasons patients cannot be kept under the strictest supervision, I feel that the publication of reports on its toxic effects may act as a deterrent to its use in the treatment of rheumatoid arthritis. In its place one would recommend aspirin, given in maximum tolerated doses as described in the recent Medical Research Council and Nuffield Foundation Report (1954).

Phenylbutazone, however, would appear to be an effective therapeutic agent in the acute stages of gout (Huffman *et al.*, 1954) on which it has a marked uricosuric effect. The majority of acute attacks of gout are brought under control within 8–12 hours, and the drug need be given only for a matter of days, thus greatly reducing the danger of side-effects.

Summary

The literature on the toxic effects of phenylbutazone therapy in rheumatoid arthritis is briefly reviewed.

A fatal case is reported in which six complications developed during the administration of the drug—namely, ulceration of the lips and mouth, a rash, haematemesis, perforation of a gastric ulcer, jaundice, and a polyneuritis—and their causal relationship to the use of the drug is discussed.

The possible factors in the production of side-effects are mentioned.

It is felt that phenylbutazone is a dangerous drug and should not be employed in the treatment of rheumatoid arthritis, and that aspirin given in maximum tolerated doses is as effective and much less toxic.

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