hepatocellular damage was seen in all six cases biopsied, but cholestasis was seen in only two of them. In this respect our findings are in conformity with the biochemical observations of Eisalo and of Palva and Mustala, in that abnormal enzyme levels are seen more frequently than abnormal biliary excretion tests.

According to Eisalo *et al.* the biochemical changes of liver damage at contraceptive dose levels are transient, lasting only one to four weeks. The transaminase levels return to normal even when administration of the drug is continued. The recognition of these changes therefore requires repeated determinations in the first few weeks of drug administration—and this may be the reason for its failure to be recognized in some of the series mentioned at the beginning of this paper. However, at the higher dosage given in our series the raised transaminase levels continued throughout treatment.

The presence of an alkylated group in the C17 position is the steroid configuration which is apt to induce hepatic damage and cholestasis when the drug is given in sufficient dosage for prolonged periods (Sherlock, 1963). Both the progestogen and the oestrogen components of Lyndiol possess this configuration, and in our restricted series the combination of the two hormones caused considerably more liver damage than either alone. This is in conformity with Eisalo's findings.

It has been suggested that there is synergic toxicity of the two components (Borglin, 1965). This is not proved, and the greater damage observed when they are combined may be purely an additive effect. At contraceptive dose levels Eisalo found a rise in transaminase levels from the progestogen component alone in only one out of 25 cases. At our dose level we found such changes in three out of seven cases, associated with parenchymal cell necrosis. Hepatotoxic changes following the administration of progestogens are probably therefore dose dependent. From Eisalo's reports (1964, 1965), it might be deduced also that for the same dose the hepatotoxic effect is greater in the post-menopausal than the pre-menopausal patient.

SUMMARY

A correlation has been established between raised serum glutamic oxalacetic transaminase levels and histological evidence of hepatocellular damage in a series of four post-menopausal patients treated by Lyndiol and seven patients treated by lynoestrenol, its progestogen component. Histological evidence of hepatocanalicular damage in a proportion of cases has also been demonstrated, but this does not appear to run parallel to changes in the transaminase levels. Raised enzyme levels persisted for many months when drug dosage at high levels was maintained.

Mestranol, which is the oestrogen component of Lyndiol, caused no abnormality in biochemical liver tests in the four patients studied.

The results suggest that the hepatotoxic effects of oral contraceptives are mainly due to their progestogen content.

BASIL A. STOLL, F.F.R., D.M.R.D.&T., M.R.C.S.,
J. T. ANDREWS,* M.R.A.C.P., M.C.R.A., D.OBST.R.C.O.G.,
R. MOTTERAM, M.B., B.S., B.SC., M.R.A.C.P., M.C.P.A.,
Peter MacCallum Clinic, Melbourne.

* Now Medical Officer to Radioisotope Unit, Royal Melbourne Hospital, Melbourne.

REFERENCES

Bakke, J. L. (1965). *Brit. med. J.*, **1**, 631.
Borglin, N. E. (1965). Ibid., **1**, 1289.
Brain, Lord, Parkes, A. S., and Bishop, P. M. F. (1964). *Lancet*, **2**, 1329.
Carlström, H., Höglund, S., and Reizenstein, P. (1965). *Brit. med. J.*, **1**, 993.
Cullberg, G., Lundström, R., and Stenram, U. (1965). Ibid., **1**, 695.
Eisalo, A., Järvinen, P. A., and Luukkainen, T. (1964). Ibid., **2**, 426.
—— —— —— (1965). Ibid., **1**, 1416.
Larsson-Cohn, U. (1965). Ibid. **1**, 1414.
Linthorst, G. (1964). Ibid., **2**, 920.
Marquardt, G. H., and Fisher, C. I. (1961). *J. Amer. med. Ass.*, **175**, 85.
Palva, I. P., and Mustala, O. O. (1964). *Brit. med. J.*, **2**, 688.
Rice-Wray, E. (1964). Ibid., **2**, 1011.
Schaffner, F., Popper, H., and Chesrow, E. (1959). *Amer. J. Med.*, **26**, 249.
Sherlock, S. (1963). *Diseases of Liver and Biliary System*, 3rd ed. Blackwell, Oxford.
Sotaniemi, E., Kreus, K. E., and Scheinin, T. M. (1964). *Brit. med. J.*, **2**, 1264.
Stoll, B. A., Andrews, J. T., Motteram, R., and Upfill, J. (1965). Ibid., **1**, 723.
Swaab, L. I. (1964). Ibid., **2**, 755.
Swyer, G. I. M., and Little, V. (1965). Ibid., **1**, 1412.
Tyler, E. T. (1964). Ibid., **2**, 1264.
Werner, S. C. (1947). *Amer. J. Med.*, **3**, 52.

Medical Memoranda

Activation of Latent Infection by Indomethacin: a Report of Three Cases

Brit. med. J., 1966, **1**, 961–962

Indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid, is a potent, non-steroid, anti-inflammatory agent which has given encouraging results in the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and gout (Hart and Boardman, 1963). Since its introduction in 1963 it has been used with increasing frequency and is now prescribed in this hospital more often than any other anti-rheumatic drug except aspirin.

Toxic side-effects are common with indomethacin. In the early trials the use of the compressed tablet and excessively high doses (200–300 mg. daily) often resulted in serious complications such as gastro-intestinal haemorrhages and perforated peptic ulcer (Norcross, 1963 ; Lövgren and Allander, 1964 ; Wanka *et al.*, 1964). With the use of the drug in powder form in gelatin capsules and doses of 75–100 mg. daily serious side-effects have been reduced, though by no means eliminated, and the milder complaints such as headache, faintness, drowsiness and giddiness, and nausea and dyspepsia, though still relatively common, are usually not serious enough to necessitate withdrawal of the drug.

In spite of the known tendency for the more potent anti-inflammatory compounds to cause a flare-up of existing but controlled infection, there has so far been no report of this complication occurring with indomethacin. Three such cases have now been encountered in this unit and are described below.

CASE 1

A shopkeeper aged 39 was admitted to hospital for a right inguinal herniorrhaphy. Soon after the operation he

developed pain in the right hip which became progressively worse over the next two months.

Examination then revealed a 35° flexion deformity of the right hip with movements markedly restricted in every direction. The herniorrhaphy scar had healed and general examination showed no other abnormality. He was apyrexial and his pulse rate was normal.

Radiographic examination of the hip showed a slight blurring of the outlines of the femoral and acetabular articular surfaces but no active bone destruction or erosion. The appearances were compatible with either a low-grade infection of the joint or rheumatoid arthritis.

The sedimentation rate (Wintrobe) was 5 mm./hr. The blood picture was normal. Blood cultures and tests for typhoid and brucellosis were negative. The Mantoux test was negative. Plasma uric acid was 6.8 mg./100 ml. The sheep cell agglutination test was negative but the latex fixation test was positive; C-reaction protein was 2-plus positive. On being repeated, the latex fixation test was negative.

Two weeks after admission, when the patient's condition was unchanged and he was still being investigated, he was inadvertently included in a group of patients to be treated with indomethacin. After receiving 100 mg. daily for six days he suddenly became very ill, his temperature rose to 100° F. (37.8° C.), and the hip became excruciatingly painful, with passive movements now quite impossible. A further radiograph showed deterioration of the joint with bone destruction along the articular margin of the femur.

Open drainage of the hip and synovial biopsy were carried out forthwith. Thin pus and flakes of caseous material were encountered in the joint.

Histological examination of the synovium showed a granulomatous reaction consistent with tuberculosis, and occasional acid-fast bacilli. Mycobacteria were later cultured from the pus.

Case 2

A manufacturer aged 28 sustained a fracture-dislocation of the right hip in a motor accident in May 1960. The hip was reduced by open operation and a large displaced acetabular fragment was fixed back in position with two screws. After six weeks in a plaster-of-Paris spica he was discharged.

During the next four years he had almost constant mild pain in the hip, with occasional more severe episodes, one of which (in 1962) was associated with a pyrexial illness lasting four days.

In April 1965, 10 days before admission to this unit, he was put on to indomethacin, 100 mg. daily, for the pain in his hip. There was dramatic symptomatic improvement within the first three days. On the eighth day of this treatment, however, he suddenly became severely ill and the pain in his hip recurred with greater severity than ever before.

On admission to hospital his condition was alarming. He was mentally confused, with a temperature of 103° F. (39.4° C.) and a pulse rate of 136. He was dyspnoeic and had all the signs of a bilateral pneumonia. The right hip was held rigid and even the slightest movement caused intense pain.

Radiographic examination of the lungs showed widespread areas of consolidation. Radiographs of the hip showed some blurring of joint outline but no bone destruction.

The haemoglobin estimation was 14.5 g./100 ml., the white cell count 16,000 per c.mm., and the sedimentation rate 20 mm. (Wintrobe). Blood culture produced a growth of coagulase positive *Staphylococcus aureus*. Vigorous antibiotic treatment resulted in a gradual return to his previous state.

Case 3

A 63-year-old housewife with long-standing rheumatoid arthritis began to complain of increasing joint pains. Five years before this a similar exacerbation in activity of the disease had been treated by steroids—with disastrous effect, for soon after commencing this treatment she developed a septic arthritis of the right hip-joint. After open drainage of the pus and prolonged antibiotic therapy the infection subsided in the hip, only to recur in the left shoulder. A further course of antibiotics and drainage of pus were required, after which her condition slowly returned to its previous state.

Thereafter any sign of recurring activity of the rheumatoid arthritis was treated with considerable circumspection, and steroids were not used again. At the start of the present attack, however, she was put on to indomethacin, 100 mg. daily. Ten days later she developed severe dyspepsia, and three days after that she complained of intense pain and swelling of the left elbow. On examination she was found to have a septic arthritis of the left elbow-joint. The indomethacin was stopped, she was given erythromycin in large doses, and the arm was splinted to control pain. After three weeks it settled down again and soon afterwards the antibiotic was discontinued. Her symptoms have not recurred for over three months.

Comment

The anti-inflammatory action of indomethacin, as evidenced by the inhibition of cotton-pellet granuloma formation in the rat, is considerably stronger than that of either phenylbutazone or hydrocortisone (Winter *et al.*, 1963). Yet, in contrast to hydrocortisone, indomethacin has been shown not to diminish the resistance to infection in the experimental animal, even when given in amounts 100 to 300 times the threshold dose for effective anti-inflammatory activity (Merck Sharp and Dohme, 1964). When, therefore, one considers that the reported incidence of intercurrent infection in humans treated with steroids is far lower than might be expected from the experimental findings (Benedek and Montgomery, 1954; Bennett *et al.*, 1964), it is tempting to discount the possibility of this complication altogether in the case of indomethacin.

The three cases described here invite a reassessment of this precept. In Case 1 a covert infection was brought to light and in Cases 2 and 3 a known or suspected previous infection was reactivated after the administration of indomethacin. Whereas hydrocortisone causes a reduction in antibody formation and phagocytic activity, indomethacin does not produce either of these effects (Merck Sharp and Dohme, 1964). It is presumed, therefore, that the complication encountered in these three cases was due to a breakdown of the local barriers to the spread of infection. This is cause for disquiet and points to the need for further investigation of the effects of indomethacin and greater care in the selection of patients for treatment with a potent drug which is being prescribed with the current abandon.

I would like to thank Mr. S. Sacks and Mr. H. Klein for allowing me to publish the details of Cases 2 and 3 respectively.

L. Solomon, M.D., F.R.C.S.,
Rheumatism and Arthritis Unit,
Johannesburg General Hospital, South Africa.

References

Benedek, T. G., and Montgomery, M. M. (1954). *J. Lab. clin. Med.*, **44**, 766.
Bennett, I. L., Finland, M., Hamburger, M., Kass, E. H., Lepper, M., and Waisbren, B. A. (1964). In *Year Book of Medicine, 1963-1964*, edited by P. B. Beeson, C. Muschenheim, W. B. Castle, T. R. Harrison, F. J. Ingelfinger, and P. K. Bondy, p. 36. Year Book Medical Publishers, Chicago.
Hart, F. D., and Boardman, P. L. (1963). *Brit. med. J.*, **2**, 965.
Lövgren, O., and Allander, E. (1964). Ibid., **1**, 118.
Merck Sharp and Dohme (1964). *Report on Indomethacin and Infection*, Merck Institute for Therapeutic Research, Rahway, New Jersey.
Norcross, B. M. (1963). *Arthr. and Rheum.*, **6**, 290.
Wanka, J., Jones, L. I., Wood, P. H. N., and Dixon, A. St. J. (1964). *Ann. rheum. Dis.*, **23**, 218.
Winter, C. A., Risley, E. A., and Nuss, G. W. (1963). *J. Pharmacol. exp. Ther.*, **141**, 369.