We found pain referred to the arm above the wrist in 14 cases. It was on occasion felt as far up as the shoulder. The following is an illustrative case.

This patient had typical nocturnal paraesthesiae in the left hand. She also had wasting of the thenar muscles of moderate degree and impairment of sensation to pin-prick and light touch, not confined to the median area but extending up the radial side of the forearm almost to the elbow. An area of sensory impairment of this size seemed to rule out carpal tunnel compression, but in view of the typical symptoms the transverse carpal ligament was divided. The symptoms were immediately relieved; wasting and sensory impairment cleared up slowly over some months—eventually completely.

Garland *et al.* (1957) say that they compressed the anterior aspect of the wrist digitally for three minutes in five patients and reproduced typical acroparaesthesiae in three. One of us (F. R. Z.) used a similar test. Firm pressure over the transverse carpal ligament for one to three minutes reproduced the typical paraesthesiae in 22 out of 27 patients in this series. However, the most important single diagnostic feature was tingling often amounting to pain in the thumb and radial three fingers, worse in bed at night, and improving after the patient had been up and about for several minutes. Where this history was given, division of the transverse carpal ligament brought complete relief of symptoms even if the pain present in the arm had spread as far as the shoulder.

Discussion

From our experience and also from that of Kremer *et al.* (1953), Garland *et al.* (1957), and Heathfield (1957) it is clear that the original description must be widened to include cases which, while having the typical pain and paraesthesiae, also have wasting of the thenar muscles, impaired sensation in the median area, and pain spreading upwards from the hands even as far as the shoulder.

In 1947 Brain *et al.* described six cases of compression of the median nerve in the carpal tunnel. At least three of these cases had the typical acroparaesthesiae as well as wasting of the thenar muscles and sensory loss. It would appear that these represent more severe cases of the "acroparaesthesiae syndrome."

The onset of the syndrome is often associated with undue fatigue—for example, after carrying very heavy shopping baskets. It therefore seems possible that some form of compression of the venous return is taking place at the thoracic inlet, giving rise to undue swelling of the soft tissues distal to the carpal ligament.

Three years ago we saw a woman with typical acroparaesthesiae. The symptoms had been present only three weeks and cleared up completely with rest. Four months ago we again saw this patient with severe acroparaesthesiae in the right hand, much less in the left. She also had severe pain in the forefinger which was present day and night and prevented sleep. Instead of the normal joints and hands of three years before, she now had the typical early menopausal rheumatoid type of arthritis with a good deal of soft-tissue swelling in the hands and wrists. The pain was so severe that the right transverse carpal ligament was divided. There was immediate relief of the severe pain and paraesthesiae, though the rheumatoid process remained unchanged.

This case is not included in the above series as insufficient time has elapsed for a follow-up. It seems fairly clear in this case that soft-tissue swelling below and distal to the carpal ligament was to some extent responsible for undue pressure on the median nerve by the carpal ligament. Why, therefore, do we not see this syndrome more commonly in rheumatoid arthritis? Whether any such mechanism as this plays a part in producing symptoms in what appears to be an otherwise normal hand is at the moment speculative, but there can be no doubt that our results strongly support McArdle's (1951) original view.

Summary

In 30 cases of acroparaesthesiae the transverse carpal ligament has been divided in 34 wrists. In 33 there was immediate relief of pain and paraesthesiae. In the remaining case some other pathological condition was present.

Wasting of the thenar muscles, impairment of sensation, and pain referred to the arm, even as far as the shoulder, have been present in these cases—apparently successfully treated by division of the anterior carpal ligament.

REFERENCES

- Brain, W. R., Wright, A. D., and Wilkinson, M. (1947). *Lancet*, 1, 277.
 Ford, F. R. (1956). *Johns Hopk. Hosp. Bull.*, 98, 464.
 Garland, H., Bradshaw, J. J. P., and Clark, J. M. P. (1957). *Brit. med. J.*, 1, 730.
 Heathfield, K. W. G. (1957). *Lancet*, 2, 663.
 Kellgren, J. H., and Moore, R. (1952). *Brit. med. J.*, 1, 181.
 Kremer, M., Gilliat, R. W., Golding, J. S. R., and Wilson, T. G. (1953). *Lancet*, 2, 590.
 McArdle, M. J. (1951). Oral communication to the Association of British Neurologists, October, 1951.
 Martin, J. P., and Elkington, J. St. C. (1955). In *Price's Textbook of the Practice of Medicine*, 9th ed., p. 1581. Oxford.
 Price, F. W. (1950). *Textbook of the Practice of Medicine*, 8th ed., p. 1151.
 Schultze, F. (1893). *Dtsch. Z. Nervenheilk.*, 3, 300.
 Walshe, F. M. R. (1945). *Brit. med. J.*, 2, 596.
 — (1951). In A. Felling's *Modern Trends in Neurology*, chap. 17, p. 542. Butterworth, London.
 — (1955). *Diseases of the Nervous System*, 8th ed. Livingstone, Edinburgh.

Medical Memoranda

Fatal Case of Agranulocytosis Due to Chlorpromazine

Jaundice and photosensitization of the skin are well-recognized complications of chlorpromazine therapy. Neutropenia and agranulocytosis occur more commonly in cases treated with another phenothiazine compound, pectazine ("pacatal") (Mitchell *et al.*, 1957), but at least two fatal cases of agranulocytosis following treatment with chlorpromazine have already been reported (Tasker, 1955; Pollack, 1955). A brief account of yet another fatal case of agranulocytosis following treatment with chlorpromazine is given below.

CASE REPORT

The patient, a man of 47, was formerly a collier and later a pottery worker. He developed symptoms of schizophrenia while serving in Egypt in 1943, and was sent back to England shortly afterwards. He was an in-patient at St. Edward's Mental Hospital, Cheddleton, almost continuously since then. He was disturbed by visual hallucinations, laboured under various delusions, and attempted to commit suicide. No remission or improvement of his mental symptoms occurred. A blood count taken on March 29, 1957, was quite normal. Next day treatment with chlorpromazine was begun, starting with 75 mg. daily and gradually increasing to 300 mg. daily. On June 17, while still receiving the same dosage, he developed a sore throat and a pyrexia of 104° F. (40° C.). His white cell count was 250 per c.mm., with complete absence of neutrophils. A diagnosis of agranulocytosis was made, the drug withdrawn immediately, and treatment with penicillin instituted. As his general condition deteriorated he was transferred to the City General Hospital, Stoke-on-Trent, where on arrival on June 19 his blood count showed 105% haemoglobin (15.5 g./100 ml.), with a total white cell count of 300 per c.mm. and a complete absence of neutrophils. Jaundice and bronchopneumonia supervened 24 hours later, and he died on June 21, four days after the onset of symptoms.

Necropsy, performed 22 hours after death, revealed generalized icterus of skin, sclerae, and most of the internal

organs. The liver (weight 2,090 g.) was somewhat enlarged and oedematous. Microscopical examination showed mild fatty degeneration and a scanty infiltrate of lymphocytes in the portal tracts. The trachea and main bronchi contained mucopus, and both lobes of the left lung were consolidated. The microscopical picture was that of pneumonia, though only very few polymorphs were found in the inflammatory exudate. There were numerous ulcers in both tonsils and at the base of the tongue. Histological sections showed massive necrosis in the floor of these ulcers, but again there were only very few neutrophils. The bone marrow of the sternum, the vertebral column, and several long bones appeared normal to the naked eye, but smears and sections revealed a complete absence of all myeloid cells, with the exception of a few scattered promyelocytes and eosinophilic myelocytes. The bulk of the cells were erythroblasts and lymphocytes, with a normal distribution of megakaryocytes.

COMMENT

The cause of death was undoubtedly agranulocytosis and pneumonia. Jaundice develops in many cases of agranulocytosis from all causes, usually as a terminal event. It is therefore difficult to say in this case whether it was due to liver damage from chlorpromazine or to the agranulocytosis.

It is generally agreed nowadays ("Any Questions," 1957) that regular blood counts can do little to prevent agranulocytosis due to drug therapy. The present case therefore underlines once again the need for caution in the administration of drugs of the phenothiazine group.

Our thanks are due to Drs. C. H. Catlin and J. H. Molloy, under whose care the patient was admitted.

C. GILES, M.D., B.Sc.,
Consultant Pathologist.

R. VEREKER, M.D., D.P.M.,
Consultant Psychiatrist.

REFERENCES

- "Any Questions?" (1957). *Brit. med. J.*, 1, 1195.
Mitchell, P. H., Sykes, P., and King, A. (1957). *Ibid.*, 1, 204.
Pollock, B. (1955). *Psychiat. Quart.*, 29, 439.
Tasker, J. R. (1955). *Brit. med. J.*, 1, 950.

Intra-articular Prednisolone

Although prednisolone (Δ^1 -dehydro-hydrocortisone) has been available for systemic administration for several years, it is only recently that it has been prepared in a form suitable for intra-articular injection.

So far only three reports have been published on its use by this means. Hagedorn (1957), in surveying the results of its administration to 89 patients suffering from various joint and periarticular soft-tissue lesions, concludes that it produces the same effect as hydrocortisone in less than half the dosage. Moreover, he states that it is completely free of the local exacerbation of symptoms that is known to follow the local use of hydrocortisone in 25 to 30% of cases. On account of this complete absence of subjective and objective side-effects, the small doses needed, and the fact that the effect of prednisolone is equal to that of hydrocortisone, he concludes that it is the drug of choice. Thompson (1957) and Newton (1957), although not quoting the number of cases subjected to trial, suggest that there is no significant difference between prednisolone in its acetate or higher ester form and hydrocortisone, although Thompson considered that the results were significantly better when it was injected into the small joints of the hand.

PRESENT INVESTIGATION

In view of this apparent contradiction of evidence the results of a short controlled trial of prednisolone acetate ("hydrodeltalone") in 79 patients suffering from rheumatoid arthritis are recorded. The difficulty in assessing results in

this condition was to some extent eliminated by confining the trial to the elbow- and knee-joints, both of which are readily accessible to measurement of joint swelling, joint temperature, and range of movement. The trial was also confined to joints in the acute stage, as, although the steroids could be expected to produce only a temporary relief of symptoms, this period of relief could be accurately measured in days or hours. Eighty patients were accordingly selected and injected with equal doses (25 mg.) of either hydrocortisone or prednisolone acetate at random. After the effect of one injection had been judged to have worn off, the other steroid was injected. At the time of the injection with the prednisolone the patients were not told that a "new drug" was being tried, and to all external appearances the content of the syringe appeared the same in each case.

Every patient was asked to give an assessment upon the speed of the effect, the incidence of local reaction to the injection, and the duration of the effect.

This inquiry was correlated with a subjective examination of the joint involved to estimate improvement in swelling and range of movement.

Results.—Of the 80 patients treated in the manner described, one failed to return for assessment and six have been excluded from analysis as they failed to show any response to hydrocortisone, although all responded to the

Results

Drug	Average Onset of Relief	Average Duration of Relief	No. of Patients with Increased Joint Pain
Hydrocortisone ..	30 hours	6.5 days	38
Prednisolone ..	20.3 "	8.1 "	15

prednisolone. The results in the remaining 73 patients are shown in the Table. The average onset of relief was 10 hours earlier in the case of prednisolone, the average duration of relief two days longer, and the incidence of side-effects 27% lower. There seemed to be little difference in the intensity of the effect between the two drugs in similar doses. Statistical analysis of the results by 2×2 contingency confirms the clinical impression that prednisolone produces the more rapid and longer duration of relief than hydrocortisone ($\chi^2 > 11$, $P = 0.001$).

CONCLUSIONS

It would appear, therefore, that prednisolone acetate gives a significantly longer period of relief, a much lower incidence of local reaction, and a slightly more rapid onset of effect in the acutely inflamed rheumatoid arthritic joint than hydrocortisone acetate. That six patients responded to prednisolone who were resistant to hydrocortisone would suggest that the former might prove of value where such a resistance is already known to exist.

Although the present trial was confined to those suffering from rheumatoid arthritis, experience with 284 patients suffering from a wider range of articular and soft-tissue lesions suggests that this rapidity of action, reduction in the incidence of local exacerbation, and duration of effect can also be observed following local injection of prednisolone.

I thank Dr. E. J. Crisp, consultant to the department of physical medicine, Guy's Hospital, for permission to publish these results; Dr. W. J. Butterfield for assistance in the statistical survey of the figures; and Messrs. Ward Casson Ltd. for the generous supply of hydrodeltalone.

P. HUME KENDALL, M.R.C.P., D.Phys.Med.,
Senior Registrar,
Department of Physical Medicine, Guy's Hospital, London.

REFERENCES

- Hagedorn, H. (1957). *Medizinische*, 1, 429.
Newton, D. R. L. (1957). *Brit. med. J.*, 2, 294.
Thompson, M. (1957). *Ibid.*, 2, 294.