ificantly greater rise in the patients taking ferric chelate than in the other two groups ($0.05 > P > 0.02$). The difference between the other two groups is not significant.

Prothrombin Times.—In the group of patients taking the ferric chelate there was a prolongation of prothrombin time (as estimated by Quick's one-stage method) of 0.5 second after three weeks of treatment in three patients, and of 0.5 to 1 second after six weeks in five patients. All patients had returned to normal values four weeks after cessation of treatment. None of the patients taking ferrous succinate or gluconate showed any such alteration of prothrombin time.

Side-effects.—Diarrhoea or vomiting, or both, appeared in three patients taking ferric chelate. Cases 1 and 10 had moderate diarrhoea during the first week of the trial, but this cleared spontaneously without treatment or withdrawal of the drug. Case 2 developed severe diarrhoea and vomiting during the second week of the trial, necessitating withdrawal of the drug and vigorous rehydration therapy. Pathogens were never isolated, but in view of the severity and the timing of the attack it may be that it was not due entirely to the drug. It was not thought justifiable to reintroduce the drug after this patient's recovery. Case 28, receiving ferrous gluconate, had mild diarrhoea during the first week. Side-effects were not observed in the patients taking ferrous succinate, but in Case 18 death occurred from pneumonia during the fourth week of the trial.

Discussion

The group of patients receiving ferric chelate showed a significantly greater response to treatment than did the other two groups. They were, however, receiving very much larger quantities of elemental iron (Table I), because the utilization factor used to calculate the dose was an assumed one only. It seems likely that this assumed 14% utilization was too low, and that this accounts for the superior response. That an organic ferric salt should have such a good utilization factor is of interest, and is in marked contrast with inorganic ferric salts. It will also be noted that the dose of ferrous succinate administered was half of that normally recommended (Gillhespy, 1955), yet had as good a therapeutic effect as ferrous gluconate given in standard dosage (Hein and Keibl, 1950). The choice of iron preparation for a given patient would appear to be governed less by pharmacological considerations than by such factors as gastric tolerance, and, especially in children, palatability, together with the comparative cost of dispensing.

The slight prolongation of the prothrombin time observed in half of those taking ferric chelate is difficult to explain. Prolonged hypocalcaemia has been observed in rabbits following intravenous E.D.T.A. (Watson and Blackburn 1956), but serum calcium levels cannot be affected in man by very large oral doses of the drug (Spencer *et al.*, 1956). Although the small alteration in prothrombin time seen in this group is apparently of no clinical significance, its cause has yet to be determined.

The higher incidence of diarrhoea and vomiting in the group taking ferric chelate must also be noted. This is no isolated occurrence, since it was found in preliminary trials with the drug; large doses were taken by my colleagues and myself over several weeks, and all noted some diarrhoea. Prothrombin times were not reduced by more than the one second reported in this trial. The diarrhoea may in part be explained by the relatively large amounts of iron in the doses given, and it would seem reasonable to suggest that doses of ferric chelate lower than those used in this trial would produce an adequate haematinic response, with a reduction in side-effects.

Summary and Conclusions

A group of 30 children and young adults with iron deficiency were treated with elixirs of ferric chelate, ferrous gluconate, and ferrous succinate. Those receiving the ferric chelate showed a significantly greater re-

sponse in haemoglobin rise compared with the other two groups, but this was probably due to the larger amount of utilizable iron given. Diarrhoea was more prominent, and there was some lowering of the prothrombin activity in half of this group, though not of sufficient degree to be of clinical importance. The dose of ferric chelate could probably be reduced below that given in this trial and still give an adequate haematological response but with a lessened likelihood of side-effects.

I am grateful to Dr. L. T. Hilliard, superintendent of the Fountain Hospital, Tooting, for permission to treat patients under his care, and to Professor T. Crawford and Dr. J. L. Stafford for advice and criticism. The work could not have been carried out but for the co-operation of the dispensary and nursing staff of the Fountain Hospital. The sytron was kindly supplied by Parke, Davis & Co., the ferromyn by Calmic Ltd., and the ferlucon by Evans Medical Supplies Ltd.

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TREATMENT OF ANTICHOLINESTERASE POISONING

BY

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The recent work in this Establishment (Childs *et al.*, 1955; Askew, 1956, 1957) which has been concentrated upon the search for a practical chemotherapy in organophosphate poisoning has resulted in the development of a combined treatment with 2-hydroxyimino-methyl-N-methyl pyridinium iodide (P.A.M.) and atropine. This has been shown to be effective in all the common laboratory species and against several times the LD₅₀ of the more toxic organophosphates and to eliminate the necessity for artificial respiration. Recent reports from Japan (Namba and Hiraki, 1958) indicate that this treatment has now been used in organophosphate insecticide poisoning in man, in some cases with marked success.

Experiments with P2S

The latest development in these laboratories has been the use of the methane sulphonate equivalent of P.A.M., which is much more soluble than the iodide but is no less effective. We have given this the code name of P2S. Animal experiments have shown that P2S may be expected to be effective therapeutically against the common insecticides such as parathion, malathion, etc., and also against amiton when accidental poisoning has occurred in manufacture or actual use. Human tests have therefore been carried out (G. D. Wedd, H. W. Whitcher, and A. Taylor, unpublished work) in which P2S has been given by intramuscular injection of the 15% aqueous solution in doses up to 20 mg./kg. At this dosage reasonable therapeutic results have been obtained in animals. P2S has also been administered orally in capsules in doses up to 75 mg./kg. In no case have there been any deleterious effects following the administration as exemplified by clinical manifestations, by changes in E.C.G., pulse rate, or arterial blood pressure, or by alterations in the blood picture. The maximum dose of P2S so far given experimentally to one man has been 4.5 g. by mouth followed by 1 g. intramuscularly three hours later.

Further work is required before a standardized treatment can be recommended, and in any case atropine is still essential. Some of the common organophosphate insecticides, however, which themselves are relatively non-toxic to man are slowly converted in the body to very toxic substances—for example, parathion is converted into the very poisonous paraoxon. Repeated dosing with P2S and atropine may therefore be necessary to counteract the effects of successive amounts of, for example, paraoxon, as this is synthesized *in vivo* from the reservoir of parathion.

P2S tends to produce small quantities of cyanide when heated in aqueous solution, the cyanide formation being greater in neutral (pH 7) than in acid (pH 4) solution. Solid P2S decomposes when heated at 150° C. It cannot, therefore, be sterilized by heat either as the solid or in solution. However, Seitz filtration has proved satisfactory. At room temperature aqueous solutions are stable for three months provided that the pH is kept at 4. The solid appears to be stable indefinitely.

P2S plus atropine is unlikely to be effective against poisoning by phosphates in which a diaminoalkyl group is directly connected with the phosphorus atom as in O.M.P.A. or mipafox (Kewitz *et al.*, 1956).

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TWO CASES OF SUBCLAVIAN ANEURYSM ASSOCIATED WITH CERVICAL RIB

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The vascular phenomena associated with a cervical rib, though less frequently observed than the neurological complications, are sufficiently well known that considerable discussion concerning their aetiology has arisen. Coote (1861) first described a vascular complication of a cervical rib which was treated by surgery, an aneurysm of the subclavian artery being present. The infrequency of vascular symptoms was shown in a review of 716 cases of cervical rib by Halsted (1918)—only 19 (5.3%) cases exhibited purely vascular symptoms, whilst 106 had a combination of neurological and vascular phenomena. An aneurysm was present in only 27 of the 716 cases. Eden (1939), in a review of 46 published cases, noted aneurysmal dilatation in nine, while Stammers (1950) stated that such a complication was, in his experience, very rare.

Todd (1911, 1913) postulated that the vascular changes associated with a cervical rib were trophic in nature, induced by irritation of the sympathetic fibres passing in the brachial plexus. Telford and Stopford (1931) enlarged on this theory, but suggested that irritation of the sympathetic fibres produced vasospasm, the infrequency of vascular symptoms being said to result from the distribution of the sympathetic fibres in the plexus. It was suggested that vascular phenomena developed only if there was a concentration of the sympathetic fibres in the lower trunk in its inferior part, the fibres thus being more prone to irritation than in a normal plexus. Their theory was supported by the demonstration of such an arrangement in one of nine subjects studied. The majority of evidence, however,

supports the theory evolved by Lewis and Pickering (1934), who suggested that the vascular symptoms associated with a cervical rib are most probably due to local thrombosis occurring in the subclavian artery, with subsequent ejection of multiple small emboli. Such a view of the aetiology is supported by the two cases reported in this paper.

Case 1

A married woman aged 56 was admitted to hospital and was seen by me on June 17, 1949. She gave a history of sudden onset of pain in the right arm when combing her hair three months previously. The pain was followed by paraesthesia, and since that time she had had periodic attacks of pain and paraesthesia in the right arm and hand, associated with weakness of grip. She had noted some swelling at the right side of the root of the neck for the past five years.

Examination revealed a marked pallor of the distal two-thirds of all the fingers of the right hand. There was full active movement of the digits, and no muscular wasting was apparent. Immersion of the hand in warm water caused the pallor to change to a cyanotic colour. No radial pulse could be detected, but in the right side of the root of the neck a pulsatile swelling could be detected, the pulsation coinciding with the apex beat. X-ray examination revealed the presence of bilateral complete cervical rib. The Wassermann reaction was negative.

A diagnosis of subclavian aneurysm associated with a cervical rib was made, the peripheral vascular changes being thought to be due to multiple emboli, the pain and paraesthesia being ischaemic phenomena.

Operation.—On June 17 a right collar incision was made, the clavicular portion of the sterno-mastoid being partly divided and the brachial plexus exposed. The latter was found to be adherent to an aneurysm of the third part of the subclavian artery, the upper trunk passing anterior to the swelling. The plexus was mobilized and freed and the aneurysm resected, an abnormal vessel arising from its superior aspect being ligated prior to removal of the aneurysm. The anterior two-thirds of the cervical rib was excised and the wound closed. Section of the aneurysm revealed a thrombus adherent to its posterior and inferior walls.

On June 18 the hand was still cyanotic but the pain was relieved; normal colour was present on June 20. The patient was discharged home on June 29, when hand and shoulder movements were normal in range and power. No untoward symptoms were present on examination two months later.

When reviewed on April 13, 1955, the patient stated that she had not experienced any symptoms since the operation. There was no detectable difference in the temperature, colour, and muscle power of the upper limbs, but the right radial pulse was absent.

Case 2

A man aged 39 was admitted to hospital with a history of dull throbbing pain in the left forearm which began suddenly three months previously. The pain gradually extended up the arm and was accompanied by a feeling of coldness in the fingers. When the fingers were cold they were seen to be blue at their tips. Warmth relieved his symptoms, while cold had the opposite effect.

On examination the left hand was cold, clammy, and blue. While there was no wasting, the grip of the left hand was markedly impaired as compared with that of the right. Sensation to touch, pain, and temperature was normal. A pulsatile swelling was present in the left side of the root of the neck. The Wassermann reaction was negative. X-ray examination revealed the presence of a bilateral complete cervical rib.

A diagnosis of subclavian aneurysm with embolic phenomena associated with a cervical rib was made and operation advised.