Fairly uniform amelioration of his rigidity brought much satisfaction, although tremor was not noticeably abated and an excess of mouth-dribbling demanded the addition of belladonna. This patient, whose general physical state was below normal, developed an anaemia which responded to iron. He complained also of transient blurring of vision while receiving diparcol.

Conclusions

Diparcol seems to offer some advantages over the tropane series of alkaloids (exemplified by stramonium) in the treatment of Parkinsonism of all grades.

It is advisable to start with small doses, and gradually to increase dosage up to a maximum of 1 g. daily until significant benefit is obtained. Withdrawal of the solanaceous drugs should be correspondingly slow; indeed, it is probably wise not to deprive patients of belladonna or stramonium completely.

It was found that treatment with two 0.25-g. tablets upon waking, followed by one tablet at noon and one at about 5 p.m., brought the greatest reduction of rigidity, there commonly being a spontaneous improvement (apart from treatment) in the evening.

Summary

The advantageous and untoward results of the drug diparcol in the treatment of eight cases of Parkinsonism are reported, and the use of the drug is discussed.

A method of recording and evaluating the results of treatment of patients with chronic disorders of locomotion is described.

I am happy to acknowledge my indebtedness to Drs. Snodgrass, Ostler, and Scott, under whose care the patients were treated, and to Dr. Mackay for permission to publish.

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SUCCESSFUL TREATMENT OF TYPHOID CARRIER WITH PENICILLIN AND SULPHAMERAZINE

BY

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The problem of treating the chronic faecal carrier of typhoid fever has always been unsatisfactory. Infection of the gall-bladder (Boyd, 1944) is one of the most important features of the chronic carrier state. It forms the basis for advising cholecystectomy in an effort to eradicate bowel infection in chronic faecal carriers; but cholecystectomy is not uniformly successful for this purpose, and there are many who have submitted to the operation without deriving the anticipated benefit. It is clear that the gall-bladder is not the only focus in the alimentary tract where chronic infection can reside for many years.

The combination of sulphathiazole and penicillin was advocated by Bigger (1946), who noted, during *in vitro*

experiments, that a combination of 4 units of penicillin and 10 mg. of sulphathiazole per 100 ml. would sterilize broth containing 70,000 typhoid bacilli per ml., and that one unit of penicillin and 10 mg. of sulphathiazole would sterilize broth containing 7,000 typhoid bacilli per ml.

Based upon Bigger's observations, the combination of penicillin and sulphathiazole has been tried during the acute typhoid illness and upon the chronic carrier state. The result of therapy during the acute illness has been disappointing; some observers record no improvement, though McSweeney (1946) noted that the toxæmia appeared to be lessened and that there were no complications due to ulceration of the bowel.

The successful treatment of two chronic faecal typhoid carriers, one of whom had previously submitted to cholecystectomy without change in his carrier state, was reported by Comerford, Richmond, and Kay (1946), who subsequently had the opportunity of carrying out a necropsy (Comerford, Richmond, and Kay, 1947) upon one of these patients who died from an unconnected cause. No cultures of *Salmonella typhi* were obtained from gut, biliary tract, urinary tracts, spleen, or lungs.

Fry, Jones, Moore, Parker, and Thomson (1948) treated 17 faecal typhoid carriers with massive doses of penicillin and moderate doses of sulphathiazole. They reported apparent cure in only three cases.

We would like to record a case treated with two separate courses of penicillin and sulpha drug, in which failure attended the first course, when the blood level of sulpha drug was low, and success followed the second course, in which it was high; the total penicillin dosage was practically the same in each course. It seems possible that previous failures by one of us (C.A.R.) in similar cases may be explained by an inadequate blood concentration of sulpha drug.

Case Report

A corporal aged 24 contracted severe typhoid fever in Egypt in January, 1946. He developed a faecal carrier state, for which he was given full doses of sulphathiazole (the exact amount was not stated), but there was no change in his carrier state. He was released from the R.A.F. eight months later, and was notified to his M.O.H. as a faecal carrier. He rejoined the R.A.F. the following year without disclosing that he was a chronic carrier. He had remained well, and had put on 2 stone (12.7 kg.) in weight.

In November, 1947, when examined for fitness for service abroad, he volunteered the information that he was a chronic carrier. His stool culture yielded a profuse growth of *Salm. typhi*, and he was admitted to this hospital. He was physically fit. Blood sedimentation rate, 3 mm. in 1 hour (Westergren). Fourteen daily specimens of urine yielded no typhoid bacilli. *Salm. typhi* was isolated from his bile obtained by duodenal intubation, and from consecutive specimens of faeces. Agglutinations were negative with "O" suspensions of *Salm. typhi* and *Salm. paratyphi* A and B, but gave a 1 in 20 agglutination with a VI suspension of *Salm. typhi*.

The man was anxious to remain in the R.A.F., but considered that cholecystectomy was too high a price to pay. In view of the uncertainty of response in clearing up the carrier state by surgery his refusal seemed reasonable. It was decided to try the effect of combined sulphamezathine and penicillin. Stools were examined immediately before beginning therapy and a profuse growth of *Salm. typhi* was isolated.

He was given 500,000 units of penicillin intramuscularly at four-hourly intervals, and 2 g. of sulphamezathine orally for two doses, followed by 1 g. four-hourly to a total of 32 g. Blood levels of sulphamezathine were carried out to determine the minimum concentration, which was anticipated to occur six hours after an oral dose of the drug. This assay showed 1.5 mg. of free sulphamezathine and 1.8 mg. of total sulpha drug per 100 ml. of blood. On completion of treatment the stools yielded a profuse growth of *Salm. typhi*.

Failure was attributed to the low blood levels of sulphamerazine, and it was decided to repeat the course, using sulphamerazine in place of sulphamezathine, since it allowed higher blood concentrations to be reached without excessive dosage. For various non-medical reasons nearly two months elapsed before starting the second course on Feb. 2, 1948.

Sulphamerazine, 2 g., was given orally at eight-hourly intervals for two doses, and subsequently 1 g. eight-hourly for seven days, to a total of 25 g. Penicillin, 400,000 units intramuscularly, was given concurrently three-hourly night and day, to a total of 24,000,000 units for the same time.

Assay of the blood for penicillin, tested three hours after an injection, yielded a concentration of 3.2 units of penicillin per 100 ml. of blood.

Assay of the blood for sulphamerazine, tested at eight hours after an oral dose—i.e., just before the next dose—yielded a concentration of 12 mg. of total sulphamerazine and 7 mg. of free sulphamerazine. Stools were cultured daily for fourteen days after cessation of the course, and all were negative for *Salm. typhi*. Stool examinations were continued for the next nine months; three daily specimens were pooled and examined each week, making a total of 117 stools cultured.

All cultures were negative for *Salm. typhi*, and it seems probable that the patient has been freed from the carrier state, though he will remain under observation for a further three months to complete a year's observation. It is noteworthy that his agglutination titre against a VI suspension of *Salm. typhi* had fallen from 1 in 20 to nil.

Discussion

The largest series of faecal carriers submitted to the synergistic action of penicillin and sulphathiazole consists of 17 cases reported by Fry *et al.* (1948); of these only three remained negative for long periods—two were still negative at 36 weeks and one at 48 weeks. Eight of their failed cases received a course identical with that successfully employed by Comerford *et al.* (1946) upon two cases. Such evidence suggests that the result of treatment is capricious and unpredictable.

Success in a single case has no particular significance, and it is published only because it may draw attention to the value of estimating blood levels during treatment. It is difficult to avoid the conclusion that blood sulpha levels in excess of 10 mg. per 100 ml. may be necessary to obtain the synergistic effect of penicillin. It is possible that the same therapeutic doses may give different blood levels in different individuals, and what seems an adequate oral dose may not create an adequate blood concentration. Sulphamerazine has the merit of giving high blood levels with moderate oral doses, and it has a minimum of unpleasant side-effects.

It is suggested that in any future series of cases treated by combined penicillin and sulpha drug the blood levels should be estimated during treatment to note what relation exists between blood concentration and successful treatment.

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Executive councils are included among the bodies on whom no development charge under the provisions of the Town and Country Planning Act, 1947, will be levied. They will make no claim against the £300,000,000 provided as compensation for loss of development rights, in Part VI of that Act. Any claim which has already been submitted to the Central Land Board should be withdrawn.

"MYANESIN" IN THE TREATMENT OF TETANUS

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The use of myanesin in tetanus was reported by Belfrage (1947) in two cases. Two further cases are described below, and these may be of interest in that they throw some light on the production of haemoglobinuria, a complication which has been reported in about twenty cases after myanesin.

Pugh and Enderby (1947) observed three cases of haemoglobinuria. The first urine passed after injection was discoloured, but no haemoglobinuria was found after two days. A death from renal anoxia after use of myanesin was reported by Hewer and Woolmer (1947), but it was pointed out by Mallinson (1948) that there were reasons for considering that myanesin was not the cause of death. A number of other cases have been described, but all were symptomless and cleared up spontaneously.

Hunter and Waterfall (1948) found myanesin useful in the control of epileptiform fits, a finding which is slightly at variance with those of Berger and Bradley (1946) that myanesin in non-paralysing doses had a powerful effect on strychnine-poisoning by depressing the reflex excitability of the spinal cord, but that the relative lack of antagonism to leptazol showed the midbrain to be influenced only when large doses were given. They thought that as myanesin does not affect consciousness or cause prenarctic excitement it had no action on the cerebral cortex.

Davison (1948) suggested that the action was on the internuncial neurones in the spinal cord, because of the production of relaxation, apparently by reduction in muscle tone, without marked interference with respiration or voluntary movements. Berger and Bradley (1946) found that paralysis in animals was of longer duration in the hinder half than in the anterior portion.

Case 1

A farm labourer aged 40 suffering from tetanus was admitted to the Royal Victoria Infirmary on June 8, 1948. He had received a small splinter wound on the palm of the hand nine days before symptoms developed. A curious but probably entirely irrelevant fact was that he stated that his brother had died in childhood of "lockjaw." There was severe generalized muscular hypertonia, affecting particularly the gluteal muscles, abdominal muscles, and the muscles of respiration, and there was also very marked neck rigidity. The characteristic tetanic spasms occurred only half a dozen times. He was treated with sedatives, mainly intramuscular paraldehyde, but after about a fortnight his tolerance to these drugs had increased so much that they were practically valueless. Soon after admission, when the muscle tonus was very pronounced and was interfering greatly with respiration, he was given *d*-tubocurarine chloride ("tubarine") 7½ mg. intravenously and an equal dose intramuscularly. This abolished his muscle tonus but also paralysed all muscles of respiration. Artificial respiration was carried out with the Oxford insufflator for more than an hour. When subsequently he developed spasms these were treated with *d*-tubocurarine chloride, and artificial respiration was always necessary if sufficient was given to control the muscular movements. This was difficult, because the patient was edentulous and it was hard to secure effective inflation. On the fifth day after admission he developed a