to vascular congestion produced by this occlusion of the hepatic venous radicles. It would appear that, if the hepatic congestion is severe and prolonged, hepatic failure with jaundice, cholaemia, and death may occur in any stage of the disease (Cases 3 and 4); if it is of short duration, complete recovery may occur (Case 1); if it is moderate and prolonged, death of liver cells and fibrosis occur with the usual mechanical results of hepatic fibrosis (Case 2).

The rapidity of appearance and disappearance of ascites in acute V.O.D. and its high protein content (usually 2 to 2.5 g.%) parallel very closely the events in acute experimental ascites in animals (Schilling *et al.*, 1952). In cirrhosis from any other cause and in the cirrhosis of chronic V.O.D. it is likely that one or more of several factors might be operative together—circulatory and hydrostatic, osmotic, inflammatory, nutritional, renal, endocrine, etc. In acute V.O.D., however, it would appear that we are dealing with the immediate mechanical effects of acute hepatic congestion produced by occlusion of the hepatic veins. The liver, as it were, becomes “stuffed” with blood through this impediment to venous drainage. The hepatomegaly and ascites so produced, in the early stages of the disease at any rate, sometimes disappear as promptly as they do in the “ascitic” dog preparation with release of vena caval constriction.

Treatment

The cause is still undetermined, and the treatment necessarily remains empirical and symptomatic. The diet of these patients is invariably deficient in proteins, although there may be an adequate calorie intake. It seems reasonable that an adequate protein intake should be sought in these patients both to improve nutrition and to slow the rate of ascites accumulation. In this connexion Kark *et al.* (1951) have postulated that severe protein depletion may directly influence capillary permeability favouring augmented ascites formation. A high-protein diet with added vitamins has been our main dietary regimen to date. Many patients show a dramatic response to these measures, bed rest, limited salt intake, and adequate attention to fluid balance. The natural history of the disease, however, is not fully known, and it would appear to be so variable and unpredictable that it is difficult to assess properly the importance of any therapeutic measures. Control studies along these lines have been started.

When accumulation of ascitic fluid is excessive repeated paracenteses may be necessary. With frequent paracenteses symptoms of hyponatraemia may develop, and the serum proteins become even more depleted. We have had little experience of the use of the various surgical procedures that have been used successfully in eliminating stubborn ascites and reducing the incidence of haematemeses. Their place, however, in selected cases of portal hypertension is well established.

Summary

The clinical features of veno-occlusive disease of the liver (V.O.D.) in Jamaica are described, with details of four cases occurring in adults.

The mechanisms of hepatomegaly and ascites formation are briefly considered. It is thought that in acute cases they are the mechanical results of hepatic congestion produced by occlusion of the hepatic venous radicles. A comparison has been drawn with the experimental ascites produced by ligation of the thoracic inferior vena cava in animals.

Treatment with a high-protein diet and fluid and salt restriction is suggested. The difficulty in assessing response to treatment is stressed.

We wish to thank Professor E. K. Cruickshank for permission to publish Case 1, and Miss E. Tomlinson and the staff of the Chemical Pathology Department for doing the liver-function tests.

REFERENCES

- Asprey, G. F., and Thornton, Phyllis (1954). *W. Indian med. J.*, 3, 17.
 Bras, G., Jelliffe, D. B., and Stuart, K. L. (1954a). *Arch. Path. (Chicago)*, 57, 285.
 — (1954b). *Docum. Med. Geogr. trop. (Amst.)*, 6, 43.
 Chiari, H. (1899). *Beitr. path. Anat.*, 26, 1.
 Hill, K. R., Rhodes, K., Stafford, J. L., and Aub, R. (1953). *British Medical Journal*, 1, 117.
 Hoffbauer, F. W. (1947). *J. Amer. med. Ass.*, 134, 666.
 Jelliffe, D. B., Bras, G., and Stuart, K. L. (1954). *Ann. trop. Med. Parasit.*, 48, 386.
 Kark, R. M., Keeton, R. W., Calloway, N. O., Morey, G. R., Chapman, R. A., and Kyle, R. H. (1951). *Arch. Intern. Med.*, 88, 61.
 Rao, M. V. R. (1935). *Indian J. med. Res.*, 23, 69.
 Rhodes, K. (1954). Academic Thesis. In preparation.
 Schilling, J. A., McCoord, A. B., Clausen, S. W., Troup, S. B., and McKee, F. W. (1952). *J. clin. Invest.*, 31, 702.
 Teilum, G. (1949). *Acta path. microbiol. scand.*, 26, 157.

TREATMENT OF PARKINSONISM WITH A NEW COMPOUND (B.S. 5930)

BY

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The correct management of patients suffering from Parkinsonism in all its forms still remains one of the most difficult problems in therapeutics. Many so-called “spasmolytic” agents have been tried in this condition with variable success. Most compounds of this group have both an antihistamine and a parasympatholytic effect, and it would appear that the drugs which are most useful in the treatment of Parkinsonism are those in which the latter effect is predominant. The advent of a new compound with pronounced anti-acetylcholine activity was felt to be of considerable interest as a possible addition to the range of drugs available for the alleviation of the distressing symptoms of the Parkinson syndrome.

Pharmacology

The new compound (B.S. 5930) is β -dimethylaminoethyl-2-methylbenzhydryl hydrochloride. It belongs to a class of which the best-known example is the antihistamine agent diphenhydramine hydrochloride. This class of compound antagonizes both histamine and acetylcholine. Investigations into substitution in the benzhydryl group gave the rather unexpected result that substitution of a methyl group at the ortho (2) position produces a very much increased anti-acetylcholine effect and a very much reduced antihistamine action.

The toxicity of B.S. 5930 is about the same as that of diphenhydramine, the L.D.₅₀ in mice being approximately 200 mg./kg. subcutaneously and 25 mg./kg. intravenously.

Patients in this trial were given 150 mg. of B.S. 5930 daily, divided into three doses of 50 mg. each. In some cases the amount was increased to 250 mg. daily. If the amount was raised above 250 mg. signs of intolerance developed, including restlessness, slight blurring of vision, and nausea. Little trouble was encountered from unpleasant side-effects when the daily dose was below 250 mg. In only one instance was the daily amount

reduced below 150 mg.; this was because of acute retention of urine. The bladder emptied spontaneously on the day after stopping the tablets, and this symptom did not occur again when the drug was given in reduced dosage.

Design of the Trial

Past experience suggested that it was extremely unlikely that the drug would prove to be either effective in all cases or ineffective in all cases, and it was felt that the method of carrying out the trial should allow for clinical evaluation of

At this stage of the trial it was possible to give a clinical evaluation of the drug and to estimate its worth in relation to previous treatment. It now remained to test the validity of the assumption that in cases in the "improved" group the improvement was due to administration of the drug. In order to make this test the "improved" group was divided into two subgroups. The two subgroups were selected by one of us (A. H. R.), after careful examination of the forms, in order to keep them as balanced as possible. A card index of the patients' names was prepared and each patient was allocated a code reference. This index, together with correspondingly coded bottles of tablets, was handed to a third party, who dispensed the tablets. Whether a given patient received active or inert tablets was unknown to either the clinician (R. O. G.) or the person dispensing the tablets. After two weeks the patients were classed as either "worse" or "no worse."

Material

Of the 67 patients to whom the new drug was administered, 32 were males and 35 females. Their ages ranged from 33 to 78 years, the distribution by age groups being as follows: eight were between 31 and 40; 17 between 41 and 50; 13 between 51 and 60; 19 between 61 and 70; and 10 between 71 and 80.

There is so little established fact about the underlying aetiology of the Parkinson syndrome that it is felt that any attempt to make a detailed classification is of no practical value. The patients in this series were grouped as being post-encephalitic if there was a history of encephalitis; as arteriosclerotic if there was a demonstrable associated arteriosclerosis; as idiopathic if there was no obvious cause. There were three patients in the post-encephalitic group; 37 in the arteriosclerotic group; and 27 in the idiopathic group.

Results

Of the 75 patients chosen at random for the trial, two failed to attend the clinic. The remaining 73 patients consisted of 55 who had responded to previous treatment and 18 who had not responded (Fig. 2). After two weeks' administration of inert tablets 50 of the "responded" group were

FIG. 1.—Diagram showing method of trial.

the relationship of the new compound to other drugs as well as maintaining statistical control of the experiment. Fig. 1 illustrates the method diagrammatically.

The names of 75 patients were selected at random from a list of those attending the Parkinson Clinic at Dudley Road Hospital. Two patients failed to attend the follow-up clinics, so that the trial began with 73 patients. They had previously been treated with compounds such as benzhexol hydrochloride, ethopropazine hydrochloride, caramiphen hydrochloride, and the solanaceous alkaloids, either alone or in combination. In all cases previous therapy had continued over a long enough period for the results to be classed arbitrarily as either "responded to treatment" or "not responded to treatment."

Data on each patient were recorded on a form, and included assessment of the ability to stand unaided, to walk, to turn corners, to climb stairs, and to write; particular attention was paid to ability to perform personal management of the daily toilet and of household chores. Assessment was also made of rigidity, tremors, "tics," cramps, sialorrhoea, lacrimation, oculogyric crises, and mental state.

For the first two weeks all patients were given inert tablets resembling B.S. 5930 and were reassessed at the end of this period. Those who were in the "responded" group on previous treatment were classed as either "no worse" or "worse," and those in the "not responded" group as either "no better" or "better." Patients who had "responded" to previous therapy but were "no worse" on the inert tablets could not be regarded as having derived benefit from active treatment. In order to minimize the dilution of the final figures they were eliminated from the trial. The one patient from the "not responded" group who was "better" on the inert tablets was also eliminated for similar reasons.

The remaining patients were then given the drug. They were seen at regular intervals, and where it was felt necessary the dose was adjusted.

A preliminary assessment was made at the end of three months, and those patients who were obviously deriving no benefit from the treatment were given a final classification of "not improved" and returned to their original treatment. The others continued for a further three months, and at the end of this period they were again assessed as "improved" or "not improved."

FIG. 2.—Results of trial.

worse and five were no worse. In the "not responded" group 17 were no better and one was better on the inert tablets. Elimination of the five who were no worse and the one who was better left 67 patients still in the trial, and these were treated with B.S. 5930. At the clinical evaluation stage (line III in Fig. 2) 14 of the 50 from the "responded"

group were "not improved" and 36 were "improved"; of the 17 from the "not responded" group 7 were "improved" and 10 "not improved." Details of the clinical evaluation are given below. The 24 who were "not improved" were eliminated from the trial at this stage, leaving 43 for the validity test. Of these, one had left the district and another failed to attend the clinic, so that the actual number of patients involved in the final stage of the trial was 41. In the two subgroups 21 received active tablets and 20 received inert tablets.

In the final stage of the trial the clinician has only the choice of classifying the patient as "no worse" or "worse." On the assumption that any improvement was due to the drug and that the clinical judgment was infallible it would be expected that all patients who receive active tablets in the final stage would be classed as "no worse" and that all patients who received inert tablets would be classed as "worse." On the null hypothesis—that improvement was not due to the drug—the final assessment would be due to pure chance. In this event it would be expected that half the patients in each group would be classed as "no worse" irrespective of the type of tablet given.

At the final evaluation in this trial (line IV in Fig. 2) 19 of the 21 patients receiving active tablets were classed as "no worse" and 15 of the 20 patients receiving inert tablets were classed as "worse." On a basis of pure chance—that is, where $p=q=0.5$ —the probability of this result is given by the sum of the first eight terms of the expansion of $(0.5+0.5)^{41}$, which gives $p=1.18 \times 10^{-5}$. In other words, the chance association of maintenance or deterioration of the patients' condition with the type of tablet given could be expected to occur with this, or greater, degree of correlation about once in 80,000 trials. It is extremely unlikely, therefore, that the association is due to chance.

The question of modification of the clinical evaluation in the light of the final stage of the trial is discussed below.

Clinical Evaluation

Clinical evaluation of the effect of treatment was based on an overall review of the subjective and objective phenomena listed in the form. An attempt was made to carry out the evaluation on a points system, but the wide diversity of the presenting symptoms and the varying severity made this impracticable. On the scheme of the trial (line III in Fig. 2) the primary division was made into "improved" and "not improved." For purposes of comparison the "improved" group was arbitrarily classed as follows: "Excellent" in those cases in which the symptoms were completely alleviated or, with particular regard to tremor, were diminished to the point of no longer interfering with the patient's normal activity; "good" where there was residual tremor but not sufficient to cause serious interference with the patient's daily life; "worth while" where the residual symptoms still caused serious interference with the patient's daily life but the scope of activity, especially with respect to the ability to perform personal toilet, was increased. In the group who had responded to previous treatment, 15 were classed as excellent, 15 as good, 6 as worth while, and 14 as not improved. In the group who had not responded to previous treatment, one patient was classed as excellent, two were classed as good, four as worth while, and ten as not improved.

The results in the group who had responded to previous treatment were compared with the condition at the beginning of the trial, and it was considered that 25 were better than they had been originally, 8 were the same, and 17 were worse.

Taking into account the patients in the "not responded" group from the beginning of the trial, it was considered that 43 of the 67 patients had derived benefit from treatment and 31 were better than on any other previous treatment. It is concluded that B.S. 5930 compares favourably with other drugs for the treatment of the Parkinson syndrome, and it is

a most useful addition to the range available at the present time. This conclusion is not affected by the modification of the clinical evaluation discussed below.

Discussion

The Parkinson syndrome is an example of the type of condition of which the aetiology is far from clear. The similarity of the disabilities which bring the patient to seek medical advice results in the loose grouping together under one heading of the end-effects of a number of differing causes. Treatment of these conditions is usually directed at alleviation of the symptoms rather than the removal of the underlying cause, and, because of this, is largely empirical. It is not surprising to find that a given drug is not equally effective in all cases. On the other hand, although the drug may not alleviate the symptoms in all cases, if it has certain basic characteristics it can be expected to produce a measure of relief in some. The clinical trial of a new compound for the treatment of this type of condition should be directed at providing information of the relative efficacy in comparison with previous methods of treatment. When the number of patients in the trial is small this comparison is, of necessity, a matter for the experienced clinician. Methods of statistical control, although highly desirable, should not interfere with the clinician's freedom of action.

One method in frequent use for the trial of new compounds is the "double-blind" test, in which active and inert material is given at random without the patient knowing which he is receiving and without the clinician knowing which he is giving. It is customary to carry out this type of trial on patients attending for the first time in order to avoid any complications from the patient's having received previous treatment. Comparison with other drugs can be achieved only by considerable elaboration of the trial.

A further disadvantage of the "double-blind" test is that if the drug is effective in only relatively few cases large numbers are required for the trial to reach a level of statistical significance. In conditions of high incidence and distressing symptoms, such as the Parkinson syndrome, a drug which is genuinely effective in only 10% of cases is still of value. The results of the present trial suggest that there will be an apparent response to treatment with inert material in about 10% of cases also. Under these circumstances a "double-blind" trial would require not less than 100 patients in both the treated and untreated groups to reach the $p=0.05$ level of significance. Apart from the problem of obtaining numbers, it is extremely difficult to justify the withholding of treatment from a large number of patients for a long period of time.

The present trial was designed to obtain the maximum information from the number of patients readily available. The test of validity was made at the point where it would inconvenience the minimum number of patients.

At the end of the first stage of the trial (line II in Fig. 2) those patients who could be expected to respond to any form of treatment are revealed and eliminated from the trial. Those remaining do not respond to treatment with the inert tablets used. The elimination of the first group at this stage removes a confusing factor from the trial. The second group, however, will still include the type of patient who reacts adversely to any change of treatment. A refinement of the method would be to give patients in the "responded" group inert tablets which were similar in appearance to those they were receiving originally. The diversity of treatments received by the patients in the present series made this procedure impracticable, and as the results weigh against the new drug rather than in its favour it was not adopted.

The second stage of the trial (line III in Fig. 2) was carried out in two parts. After three months' treatment with the new compound those patients who had obviously not shown a response were returned to their original therapy and

recorded as "not improved." Those who had responded, and also the doubtful cases, remained under treatment for a further three months. The intermediate assessment was made on the grounds that effective treatment should not be withheld from the "not improved" cases. The continuation of treatment was primarily to ascertain if tolerance for the drug developed. No signs of drug tolerance were observed at the clinical evaluation stage and none have been observed since.

The final stage of the trial could be carried out in one of two ways. The essential requirement is that neither the clinician nor the patient shall know whether the tablets are active or inert. Selection of the patients for the subgroups to be given active or inert tablets may be made at random or by design. It was felt that selection should be by design in order to keep the subgroups as evenly matched as possible. The opinions of pharmacologists and other research workers were sought on this question, and it was generally agreed that selection should be by design.

At the final stage of the trial the assessment differed in seven instances from that which would have been expected if the recorded improvement had been entirely due to the use of the new drug. Analysis of these cases is of interest. Of the five patients who were "no worse" on the inert tablets, four had been classed at clinical evaluation as "worth while" and one as "good." In common with the other patients in the subgroup given inert tablets these five were returned to treatment with B.S. 5930 at the end of the two-weeks period. The four "worth-while" patients showed no appreciable difference in their condition at the next follow-up clinic. The "good" patient, after returning to the active tablets, not only stated that she felt better but also showed some objective improvement. Examination of the forms and notes of these patients suggests that the unexpected association at the final stage was due to taking too much account of the subjective phenomena at the clinical evaluation level in the case of the four "worth-while" patients and at the final assessment in the other. Both the patients who were assessed as "worse," although they had received active tablets, had been classed as "good" at the clinical evaluation. It is now felt that they should have been classed as "worth-while."

Modification of the clinical evaluation in the light of the final stage of the trial gives: from the group who had responded to previous treatment: 15 excellent, 13 good, 5 worth while, and 17 not improved; from the group who had not responded to previous treatment: 1 excellent, 2 good, 3 worth-while, and 11 not improved.

Finally, at the risk of stating the obvious, we would like to make two personal comments. Firstly, we feel that this investigation emphasizes the need for close collaboration between the clinician and the scientist, and for careful experimental design to meet particular circumstances. Secondly, we believe that clinical evaluation is still of great importance in the trial of new drugs, and that, although highly important in these trials, statistical analysis is not a substitute for clinical experience.

Summary

A new compound, B.S. 5930, has been tried in the treatment of 67 patients suffering from Parkinsonism. A clinical improvement was noted in 39 cases. The results were considered to be good or excellent in 31 cases, or 46%.

A new method of carrying out clinical trials of this type is described and its advantages are discussed.

We would like to thank Professor A. M. Boyd for permission for one of us (A. H. R.) to take part in this investigation; all those who have given valuable and helpful criticism during the course of the investigation; and Dr. C. J. Van Bortel, of Messrs. Brocades-Stheeman, for supplying the B.S. 5930 ("disipal") and inert tablets.

OPERATIVE TREATMENT OF VARICOCELE

BY

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For the treatment of varicocele Samuel Cooper, in 1828, advocated support with a suspensory bandage, the use of cold and alum lotions, and also that the blood be repeatedly taken away by means of leeches. He considered that radical cure could seldom be effected. In more recent years Everidge (1943) stated that, although the risks of operation for varicocele were almost negligible, the end-results often left much to be desired—an opinion which reflects the general feeling of dissatisfaction with the results of the operation as commonly practised to-day. Indeed, attention has been drawn to the inadvisability of operative treatment (Douglas, 1921; Campbell, 1928; Page, 1954).

The classical operation, in which a segment of the pampiniform plexus is excised between ligatures through an upper scrotal incision, has fallen into disrepute because of the common occurrence of post-operative complications. Tearing of thin-walled dilated veins often results in the formation of a haematoma, which may become infected, with consequent prolonged sepsis and delayed convalescence. Faulty estimation of the amount of venous plexus to be removed leads to the development of a hydrocele if too many veins are tied, whereas inadequate removal is followed by a recurrence of the varicocele. Because of the difficulty in identifying small arteries in the spermatic cord, the arterial blood supply of the testis may be damaged, with consequent testicular atrophy. "I think it is impossible to remove a varicocele of any size without damaging the spermatic artery" (Page, 1954).

In an attempt to avoid such complications, operations have been devised in which the spermatic veins are divided in the inguinal canal or at the internal inguinal ring. Such procedures are particularly applicable to cases in which there is a coincident inguinal hernia, but they still carry the risk of damage to the arterial blood supply and to the collateral venous return of the testis and epididymis.

The operation described in this paper is that of division of the spermatic veins, at a level 2 in. (5 cm.) above the internal inguinal ring, where the veins lie on the posterior abdominal wall. At this site impairment of testicular blood supply can be avoided.

Venous Drainage and Arterial Blood Supply of Testis and Epididymis

Venous Drainage.—The veins of the testis and epididymis form an anastomosing plexus—the pampiniform plexus—which lies in the spermatic cord. As the veins pass upwards to the internal inguinal ring they become reduced in number, and, on the posterior abdominal wall, form one or two veins which drain into the renal vein on the left side and into the inferior vena cava on the right side. In addition to this main route of drainage, secondary venous channels pass along the vas deferens to the internal iliac veins, and communications are present between the pampiniform plexus and the pudendal and circumflex systems of veins. The presence of these subsidiary routes of drainage has been confirmed in this unit by anatomical dissections and also by radiography after injection of diodone into the