Effect of Exercise

The subject is asked to take a sharp walk for about 15 minutes. Fig. 5 shows that the temperature may rise as a result by over 1° F., recovering slightly in the next half-hour. The exercise was only moderately severe as judged by the rise in pulse rate from 60 to 125. Severe exercise in a hot, humid climate may produce pronounced pyrexia.

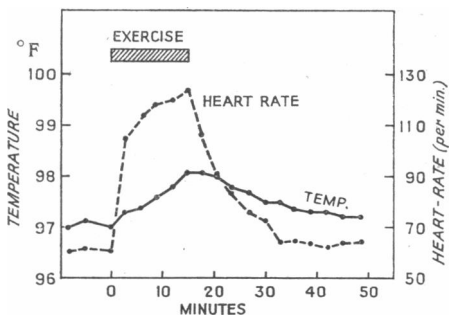

FIG. 5.—Effect of exercise on body temperature and heart rate.

Effect of (i) Standing Naked in Front of a Window for 20 Minutes and (ii) a Cold Bath

(i) These experiments were all conducted in the summer, when the external temperature was of the order of 60° F. (15.5° C.). Fig. 6*a* shows a number of results. Usually the fall of body temperature during the 20 mins. is quite small owing to compensatory mechanisms coming into action—e.g., from 98.4 to 98.2° F. (36.9 to 36.8° C.) or from 98 to 97.2° F. (36.7 to 36.2° C.) — sometimes compensation is less complete and the temperature falls to a greater extent—e.g., from 98 to 96.5° F. (36.7 to 35.85° C.). Fig. 6*a* also shows that sometimes, during the period of exposure to cold, body temperature may rise by nearly 1° F., presumably because of an overswing of the compensatory mechanisms.

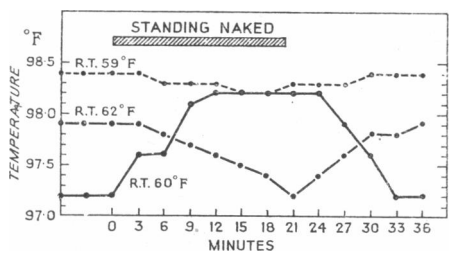

FIG. 6*a*.—Effect on body temperature of standing naked in front of an open window for 20 minutes.

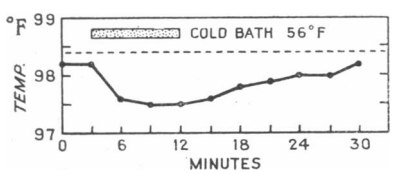

FIG. 6*b*.—Effect on body temperature of a cold bath at 56° F. (13.3° C.).

Fig. 6*b* shows the modest temperature-lowering effect of a cold bath at 56° F. (13.3° C.).

Summary

Simple experiments are described which illustrate the more important facts about normal temperature and its regulation in man.

Attention is drawn to the undesirability of having a mark on clinical thermometers opposite the 98.4° F. (36.9° C.) level, and of inscribing clinical thermometers with the words "half-minute" or "two minutes."

The Nursery School Association has started a new quarterly magazine called *Young Children* with the purpose of fostering a fuller understanding of children. The first number includes some of the evidence given by the late Dr. Susan Isaacs before the Curtis Committee. The price of the magazine is 1s. 6d.; it is obtainable from the Association at 1, Park Crescent, Portland Place, London, W.1.

USE OF DIPARCOL IN PARKINSONISM

BY

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A synthetic drug, "diparcol" (diethylaminoethyl-N-thiodiphenylamine hydrochloride), was found useful in the treatment of all forms of Parkinsonism by Sigwald *et al.* (1947) and by Bovet *et al.* (1947) in France. A limited supply was made available at this hospital by the courtesy of the manufacturers, May and Baker, Ltd., and a clinical trial of the drug was carried out in eight cases of post-encephalitic chronic Parkinsonism of varying degrees of severity. A ninth case, of malignant hypertension with the Parkinsonian syndrome, was given the drug for a short time before death; its effect, if any, could not be assessed, and the case was excluded from the series.

It is notoriously difficult to provide satisfactory criteria of change in the state of patients suffering from chronic disorders of locomotion. Evaluation of treatment therefore depends to a large extent upon the subjective opinions of the physician and of the patients and those around him, but it is advantageous to base opinions so far as is possible upon objective measurements. Carmichael and Green (1928) devised an apparatus to measure rigidity in resting limbs, and used the ergograph to record the performance of simple repetitive motions rather than of individual movements; but in the present study an attempt was made to consider each patient in terms of the following ten modal activities, which together involve automatic, impulsive, and deliberate movements of different degrees of complexity: (1) turning in bed, rising from and returning to bed; (2) dressing and undressing; (3) performance of the toilet, especially shaving in men; (4) eating; (5) walking; (6) turning around corners; (7) climbing stairs; (8) speaking; (9) writing; and (10) movements of facial expression as reflecting mood and interest.

The procedure was to observe each patient over a period of two to three months while they were receiving adequate dosage of the customary drugs (stramonium, hyoscine, belladonna) in such combination as produced the maximum benefit. In each patient the state of the ten modal activities varied, but an attempt was made to assess the efficiency of each according to the following scale:

0 = No activity on account of contractures or rigidity
1 = Activity grossly restricted or completely ineffective
2 = Moderate restriction, especially by rigidity
3 = Moderate restriction, especially by tremor
4 = Activity approaching normal, but slow and clumsy
5 = Activity practically normal, or at least effective

Throughout the test any lasting changes in the tremor or hypersalivation were recorded, but it was felt that little was to be gained from the observance of minute changes, especially in tremor, which so noticeably varies from hour to hour with the attitude and mood of the patient. In view of the failure of several authorities (Neal *et al.*, 1942) to find regular amelioration of oculogyric crises by treatment otherwise effective, a particular note was taken of the incidence of these and of "emotional" and "laryngeal" crises.

Diparcol was then given according to the scheme first recommended by the manufacturers, dosage being gradually built up over a period of five to six weeks, with simultaneous gradual withdrawal of the solanaceous drugs. Except in Case 1, the drug was given in the full dosage of 1 g. daily for a period of ten weeks, after which the effect of slightly varying the dose was studied. When the

most beneficial dosage was found, each case was reassessed in terms of the ten modal activities, and improvement or deterioration recorded. Slight improvement meant an increment of 1 unit, considerable improvement 2 units; conversely, slight deterioration was measured by a down-scaling of 1 unit, and so on. The results are shown in the table.

but were absent when the dosage was slightly reduced. (3) Paraesthesiae consisting of creeping or burning sensations referred to the head and upper trunk were mentioned by two patients. This feature tended to pass off after reassurance, despite continuance of the drug. (4) Transient blurring of vision was noted in one case. (5) Undue drowsiness was complained of by one patient; three others

Modal Activity	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8		Net Change
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	
Turning in bed	0	1	4	5	4	5	4	5	4	5	1	2	5	5	3	5	8+
Dressing and undressing	0	0	4	4	4	5	3	4	3	4	0	0	4	5	3	4	5+
Toilet	0	0	3	4	4	5	3	4	3	4	0	1	4	5	3	4	7+
Eating	0	0	4	5	4	5	3	4	3	4	0	2	4	5	3	4	8+
Walking	0	0	3	4	5	5	3	4	3	5	0	1	4	5	3	4	7+
Turning corners	0	0	3	4	4	5	2	2	3	4	0	0	4	5	3	3	4+
Climbing stairs	0	0	3	4	4	5	3	3	4	4	0	0	4	5	3	3	3+
Speaking	1	2	3	4	3	4	3	3	3	4	1	2	3	4	3	4	7+
Writing	0	0	3	3	2	2	2	2	2	2	0	0	4	4	2	3	1+
Facial expression and mood	0	0	3	4	4	5	2	3	2	3	0	2	3	4	3	4	8+
Total change in each patient	2+		8+		8+		6+		9+		8+		8+		9+		58+
Notes and clinical impressions	Died during treatment		Striking benefit		Considerable benefit		Fainting turns		Fairly severe case gaining benefit		Subjective improvement marked. Bedridden		Moderate benefit		Salivation aggravated		

A = During control period with solanaceous drugs. B = During period of administration of diparcol. 0 = No activity. 5 = Practically normal activity.

In order to reduce the suggestive influence of a new and promising treatment three patients (Cases 2, 3, and 8) were gradually returned to the former regime of the solanaceous drugs, whereupon a notable relapse occurred, while reintroduction of diparcol once more brought favourable results. The substitution of inert tablets, mixtures, or injections to provide a control in the treatment is rarely of value, inasmuch as patients with even a mild degree of Parkinsonism soon become aware of the deception.

Results of Treatment

As will be seen from the table, all the patients derived a little benefit from diparcol as compared with previous treatment. Except in Case 1, in which death occurred suddenly, the numerical benefit in each case was about equal; this contrasts with the erroneous clinical impression that had been gained that the less severely affected patients were the most improved. The reason for this impression was the striking facilitation of normal or almost normal activities in those in whom such activities had been only slightly or moderately restricted. The importance of thus evaluating and tabulating the results is manifest.

In general it would seem that the more skilled activities, such as writing, walking round corners, and climbing stairs, were improved to a smaller degree than more "primitive" acts like turning in bed or eating, but such generalizations are hardly justified in such a small series.

Improvement in the feeling of well-being was quite noteworthy in several patients; this was to some extent included in the tenth modal activity (expression).

In respect of ambulant patients any improvement, however small, in the performance of simple domestic or social tasks represents a considerable boon. The loosening up of a rigid bedridden patient, while less spectacular, was reflected in a decrease in nursing requirements.

Oculogyric crises were not significantly influenced by the drug, but in one patient there seemed to be relative freedom from "laryngeal crises" during the administration of full doses.

Undesirable Effects.—(1) Hypersalivation was not well controlled by diparcol in four of the cases, in which the addition of small doses of belladonna became necessary. (2) Faintness and "fainting turns" occurred in two patients, reported that they were sleeping better. (6) Weekly blood counts were carried out in half the cases in view of the death of one of Sigwald's patients from agranulocytosis (which was not thought to be related to treatment by the drug). There was a tendency for the white cell count to fall to 4,000 per c.mm. during the initial weeks, with subsequent rise to former levels. No case of true leucopenia occurred. In one patient a slight iron-deficiency anaemia was noted; this responded well to ferrous sulphate.

Illustrative Case Histories

Case 1.—A debilitated woman aged 30 was suffering from progressive Parkinsonism which followed an attack of encephalitis lethargica at the age of 7. She was almost completely bedridden on account of rigidity of the limbs and trunk; the upper limbs were maintained in flexion, with the lower limbs partially extended. Hypersalivation and seborrhoea were excessive, and she was subject to frequent oculogyric and laryngeal crises; speech was infrequent and practically unintelligible. After receiving diparcol for a month, with little benefit, she developed pyrexia associated with respiratory symptoms and was taken off that drug, full doses of stramonium and hyoscine being substituted. Five days later she died suddenly. Necropsy revealed only bronchopneumonia, but it was noted that rigor mortis of the viscera had persisted longer than usual. According to Hall (1943), sudden unexpected death is not rare in young women with Parkinsonism. Perhaps the sudden withdrawal of the diparcol resulted in a paroxysmal autonomic crisis leading to fatal peripheral circulatory failure and bronchopneumonia. Similar crises have been reported by Ostow (1943) and Oller (1946).

Case 2.—A labourer aged 36 first developed oculogyric crises at the age of 29, after which the full Parkinsonian picture slowly became manifest. He was ambulant, but experienced particular restriction of fine movements, largely from rigidity. His general health was good. Following treatment with diparcol he obtained uniform benefit in almost all locomotor functions, gratefully attested by his relatives. During the administration of large doses he complained of occasional paraesthesiae and faintness. Only laziness prevented him from undertaking simple remunerative employment.

Case 8.—A retired lamp-lighter aged 64 had suffered from encephalitis lethargica in 1919 at the age of 35. Considerable disability of gait had been present for at least three years, together with gross tremor and rigidity of the limbs, which considerably restricted all motor activities. Rigidity of the trunk, which prevented his turning in bed at night, was a constant source of annoyance to him before receiving diparcol.

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 wakening, 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, Oastler, and Scott, under whose care the patients were treated, and to Dr. Mackay for permission to publish.

REFERENCES

Bovet, D., Fournel, J., and Charpentier, P. (1947). *Thérapie*, **2**, 115.
Carmichael, F. A., and Green, F. H. K. (1928). *Quart. J. Med.*, **22**, 51.
Hall, Sir A. (1943). *Lancet*, **1**, 193.
Neal, J. B., *et al.* (1942). *Encephalitis: A Clinical Study*. Lewis, London.
Oller, C. I. (1946). *Arch. Neurol. Psychiat., Chicago*, **55**, 388.
Ostow, M. (1943). Ibid., **50**, 342.
Sigwald, J., Durel, P., and Dumont, G. (1947). *Thérapie*, **2**, 108.

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 toxaemia appeared to be lessened and that there were no complications due to ulcération 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*.