may suffice for mathematics and some aspects of theoretical physics. For the path of truth, even though the ultimate goal is never attained, is by observation, classification, and a reactive hypothesis; then comes the search for significant facts by further directed and controlled observation (which is experiment) which will support, modify, or refute this initial hypothesis; this leads to further hypotheses (induction) which are again tested by observation and experiment (deduction). Of this and of the unexpected result of experiments Hunter was well aware. "Many things," he observes, "arise out of investigation which were not at first conceived; and even misfortunes in experiments have brought things to our knowledge that were not, and probably could not have been, previously conceived. On the other hand, I have often devised experiments by the fire-side or in my carriage, and have also conceived the result; but when I tried the experiment the result was different, or I found the experiment could not be attended with all the circumstances that were suggested." (*P.*, IV, IX.)

Conclusion

Other orators, both of this Society and of the Royal College of Surgeons, have dealt in detail with Hunter's contributions to pathology and to the craft of surgery, and we do right to honour him with Ambroise Paré and Lister as one of the three greatest surgeons the world has known. But he surpasses them both, for he was one of the greatest experimental biologists of all time, who brought to the study of medicine not only an unrivalled knowledge of anatomy and physiology, and an unmatched industry and zest in unmasking Nature's secrets, but a supreme intellect and creative imagination yoked to the scientific method of reflective inquiry.

It has been for me a privilege, for which I am truly grateful, to convey to you my reflections on the working of John Hunter's mind. And if in expressing opinions and formulating judgments I have erred on the side of dogmatism, I pray that you will remember, what I certainly do not forget, that these reflections are those of an amateur medical historian whose interest in the genius of ancient masters, even when labelled surgeons, has never abated.

ACETAZOLAMIDE IN TREATMENT OF EPILEPSY

BY

BARBARA ANSELL, M.B., M.R.C.P.
Registrar to Department of Medicine

AND

EDWIN CLARKE, M.D., M.R.C.P.
Lecturer in Neurology
Postgraduate Medical School of London, W.12

It has long been known that starvation may help in reducing the frequency of epileptic seizures (Guelpa and Marie, 1911). On the assumption that ketosis and acidosis were responsible, the ketogenic diet was introduced and in some hands proved of value (Barborka, 1930; Keith, 1947). Cohen and Cobb (1941) had similar success with a sulphonamide used for the same purpose on the grounds that it inhibited the enzyme carbonic anhydrase, which catalyses the reversible reaction $CO_2 + H_2O \rightleftharpoons H_2CO_3$. The main result of the inhibition is an inability to form an acid urine because of reduction in the availability of the hydrogen ion, thus producing an alkaline urine containing increased amounts of sodium. The loss of fixed base results in the production of a metabolic acidosis. Recently a much more potent carbonic anhydrase inhibitor—acetazolamide ("diamox")—has been introduced, and it seemed reasonable to attempt an evaluation of its anticonvulsant properties in view of its ability to produce an acidosis.

Bergstrom *et al.* (1952), Merlis (1954), Pero (1955), Vivien (1955), Ferroni *et al.* (1955), Munoz and Gomensoro (to be published), and Lombroso *et al.* (1956) have already reported its effects in epilepsy, and the present study is a further attempt to assess its value.

Material

Twenty-six patients were treated with acetazolamide. Of these, 23 were of the idiopathic or "centrencephalic" type of epilepsy. The definitions proposed by Symonds (1954, 1955) have been employed. Thus major epilepsy included all those with grand-mal seizures, and minimal those having the classical petit-mal attack or "blank spell" as defined by Gowers (1881) as well as the akinetic and myoclonic types. Between these two extremes were a variety of seizure patterns that are best termed "minor."

There were six patients (three male and three female) aged between 12 and 31 years, suffering from major epilepsy. Five (four female and one male), aged from 5 to 36, had the minimal type. In the minor group there were four females aged from 13 to 34 years. Those with mixed idiopathic epilepsy were aged from 14 to 38 years and comprised seven females and one male; they had all been difficult to control with known anticonvulsants during the preceding year. The remaining three patients had symptomatic epilepsy of varying aetiologies, and had resisted all therapy. Initially, only those patients who were not responding to known medications were given the drug, but later it was used from the onset in nine cases. Altogether 15 patients had acetazolamide alone over periods ranging from 4 weeks to 18 months.

Method

The majority of cases were studied as out-patients, although a few began treatment while in hospital. The frequency of seizures was recorded by the patient or a relative. There was first a preliminary control period of never less than one month, during which time nine patients had no treatment, while the remaining 17 continued previous therapy which had been inadequate to control their attacks. The following rough grouping of patients was possible:—Grade I: infrequent attacks, less than one a month; Grade II: moderately frequent attacks, more frequent than in Grade I but not more than one a week; and Grade III: frequent attacks, more frequent than one a week.

Assessment of the minimal cases was more difficult, and here Grade I contained those patients who were aware of occasional attacks, Grade II those whose attacks were frequent enough to interrupt speech and other activities, and Grade III those with continuous attacks producing a state of confusion and lengthy amnesia.

Out-patients were assessed approximately once a month and in-patients once a week. If an E.E.G. had not already been carried out a recording was made before acetazolamide therapy was begun, and another during the course of treatment. The plasma bicarbonate level was estimated before and during therapy, and in many cases it was done each month.

A dose of 125 mg. of acetazolamide twice a day was added to the previous medications in the first few cases. If improvement occurred and was sustained the other drugs were gradually eliminated. In most of those deriving no benefit the dose of acetazolamide was progressively increased and adapted to the individual until it was approximately 10 mg. per kg. of body weight.

The results of treatment were graded under four headings: (1) excellent, attacks completely dispelled; (2) good, attacks markedly decreased in frequency; (3) some value, (*a*) initial reduction in the number of attacks with a return to the pre-therapy state occurring in one or two months, and (*b*) slight but maintained control of attacks; and (4) no value. In addition a subjective comparison with other drugs was made by the patient.

Results

Clinical Effects

An overall assessment of the clinical effects is given in the Table.

Effect of Acetazolamide in 26 Cases of Epilepsy

Type of Epilepsy	Results				Total
	Excellent	Good	Some Value (*a*)	No Value	
Major	3	1	2	0	6
Minimal ..	2	1	0	2	5
Minor ..	0	1	2	1	4
Mixed ..	3	2	2	1	8
Symptomatic ..	0	1	2	0	3
Total ..	8	6	8	4	26

Major, Idiopathic

Six patients were treated with acetazolamide as their sole anticonvulsant drug for a minimum of three months with doses ranging from 3 to 14 mg. per kg. of body weight. In three (two of Grade I and one of Grade II severity) the result was classed as excellent, and they have had the drug for 18 months. Two patients (Grade III) responded excellently for six and eight weeks respectively, but then returned to their previous state, and even raising the dosage to 14 mg. per kg. did not benefit them. In the following case (Grade II) the excellent result could be maintained only by increasing the dose.

Case 1.—A woman aged 31 had suffered from idiopathic major epileptic seizures for 11 years, averaging three to four fits a month, despite treatment with phenytoin sodium and phenobarbitone. They occurred most often immediately before or after her menstrual period. The E.E.G. showed generalized changes diagnostic of idiopathic epilepsy which were enhanced by overbreathing. Initially, acetazolamide proved extremely valuable and produced an excellent result for two months, followed, however, by a relapse, but with improvement on increasing the dosage (Fig. 1).

Minimal, Idiopathic

Five patients had amounts from 4 to 12 mg. per kg. over periods of 5 to 15 months. Two had other forms of medication initially, but eventually in four it was the only drug used. There was no effect at all in two cases. In three the result was excellent, two being controlled on the initial dosage, while in the third several increases were necessary to maintain improvement.

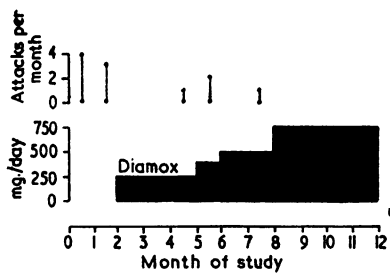

FIG. 1.—Case 1. Effect of acetazolamide alone on Grade II major epilepsy.

Case 2.—A woman aged 36 had suffered her only major seizure when 18 months old. Attacks of typical minimal epilepsy began when she was 19 and usually occurred for two days, preceding and during menstruation. At times they were so frequent that she was confused and difficult to manage. Four months before she was seen, one of these periods lasted three and a half days and thereafter the attacks became more frequent. Investigations, including an air-encephalogram, were normal except the E.E.G., which revealed spike-and-wave activity produced by overbreathing. Treatment with troxidone was begun and some improvement took place. This, however, was much increased when acetazolamide was added, and deterioration followed when the dose was reduced. Paramethadione increased the frequency of the attacks and she had a period of status during which she was confused and uncooperative. Doubling the dose of paramethadione had no effect, so acetazolamide alone was begun again at 7.5 mg. per kg. (250 mg. thrice daily). Within six hours the attacks were much fewer and after 18 they were only occasional. She has been maintained on acetazolamide alone until the time of writing (a period of 10 months), but an increasing dosage has been necessary. She then had only an occasional attack and could lead a normal life. The E.E.G. remained unchanged, but the plasma bicarbonate level was persistently low (Fig. 2).

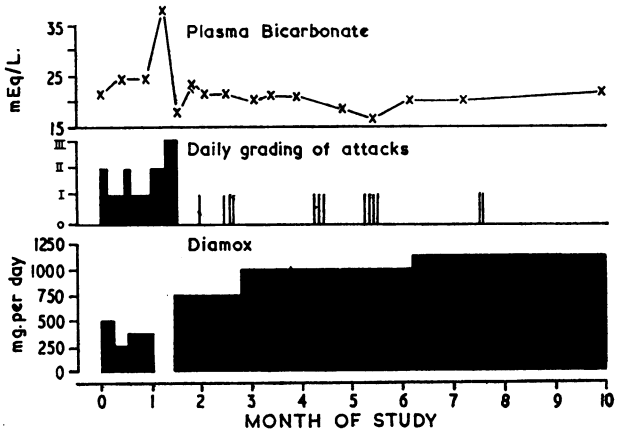

FIG. 2.—Case 2. Effect of acetazolamide alone on Grade III minimal epilepsy. For grading of attacks see text.

One patient experienced a marked increase in the frequency of his attacks (Grade III) after stopping the medication for 48 hours, and a complete relief of symptoms when it was recommenced.

Minor, Idiopathic

Acetazolamide was administered to four patients in doses of 4 to 12.5 mg. per kg. from 3 to 12 months, and in all but one of them it was the only drug employed. Only one patient had a good response, while two improved during the first month of therapy only. After an interval one of these again showed transient improvement.

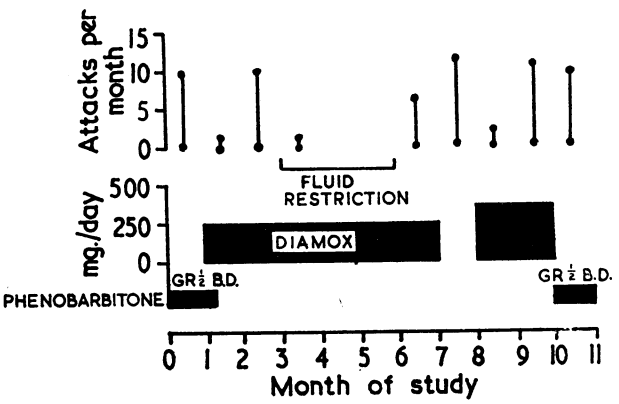

FIG. 3.—Case 3. Effect of acetazolamide alone on Grade III minor epilepsy.

Case 3.—A girl aged 18 had suffered several major seizures between the ages of 2 and 4 years. Minor epilepsy began at 11, and the attacks were almost invariably associated with menstruation. The E.E.G. showed epileptic activity enhanced by hyperventilation. The only drug that she had found of value was phenobarbitone, and so a direct comparison with it was possible.

Acetazolamide given in a dose of 5 mg. per kg. reduced the frequency of the attacks for only one month. With fluid restriction in addition, she remained much improved over three months but relapsed again when fluid restriction and then acetazolamide were omitted. Then followed four weeks without acetazolamide, with a return of fits, and eight weeks with a dose of 7.5 mg. per kg., during which time it was of value in the first month only (Fig. 3). There was no correlation between clinical and biochemical changes.

That acetazolamide was responsible for the changes in these cases is suggested by the fact that the patient with the good response omitted therapy for 10 days, during which time she had seven attacks. The following month, when she had resumed her previous dosage, she had only one attack.

Mixed Idiopathic

Treatment has been continued for periods of 1½ to 20 months in eight patients. Three, in whom there was no apparent effect at first, responded excellently when the dose was increased to 10 mg. per kg., and this effect has been maintained. In two the initial dose was of some value, but an increase to 10 mg. per kg. produced a good result, which has persisted for 18 months.

Case 4.—A man aged 38 had had severe idiopathic epilepsy of a mixed major and minimal type for nine years. It had proved extremely difficult to control, and at the time of the study he was receiving phenobarbitone, primidone, and troxidone with only partial success. The E.E.G. showed epileptic activity of a mixed type, which was enhanced by overbreathing. At first acetazolamide (3.7 mg. per kg.) was substituted for one of the five doses of troxidone he was taking. As he showed improvement, some of the other drugs were gradually withdrawn and replaced by acetazolamide, so that at the time of writing he was taking 250 mg. twice a day (7.4 mg. per kg.) and primidone thrice daily. He had then received acetazolamide for 20 months. His attacks were greatly reduced in number, although the E.E.G. was only slightly improved. The plasma bicarbonate had been maintained at approximately 27 mEq/l. (Fig. 4).

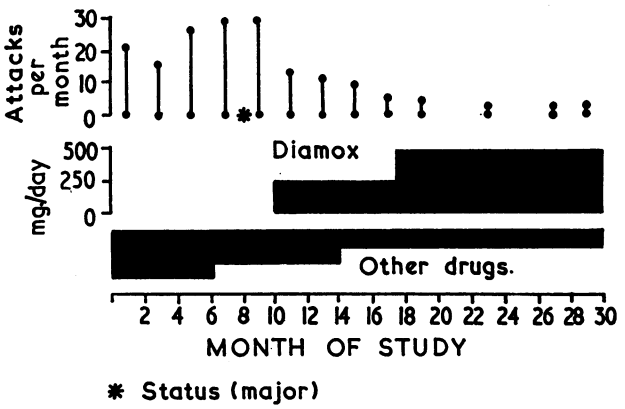

FIG. 4.—Case 4. Effect of acetazolamide as an adjuvant in Grade III mixed epilepsy.

There was considerable improvement for six weeks in a further two patients, but the deterioration that followed was not influenced by additional doses of the drug. One patient experienced no effect. It is interesting to note that in minor epilepsy alone acetazolamide appeared to be valueless, but it was of much benefit in controlling the minor attacks in the mixed idiopathic group.

Symptomatic

Where acetazolamide was used alone or as an adjuvant the result was at first good, but deterioration then occurred and an increased dosage had a favourable influence in only one of the three patients.

Effect upon Plasma Bicarbonate.—In seven cases the plasma bicarbonate content did not fall below 27 mEq/l., although each had been assessed clinically as a good result (cf. Case 4). Conversely, it was much reduced in two patients who showed no clinical effect of acetazolamide. Furthermore, deterioration could take place despite the presence of a persistently low plasma bicarbonate level. Thus there seemed to be no constant correlation between the biochemical and the clinical findings.

Effect upon the Electroencephalogram.—A total of 22 patients had a second E.E.G. carried out at some time during acetazolamide therapy. Thirteen were reported as unchanged, yet the clinical grouping was excellent in 6, good in 2, of some value in 3, and of no effect in 2. Electrical deterioration could accompany clinical improvement, and the reverse was also true. Hyperventilation was practised in most cases, but there was no correlation between the electrical response to it in the preliminary E.E.G. and the clinical results.

Comparison with Other Drugs.—Objective comparison with other drugs was possible in eight cases. In one with major seizures acetazolamide alone was better than primidone alone, during the period it was effective. In three with minimal epilepsy it was better than troxidone, in another it was inferior to phenobarbitone for a time, and in one more it was not as good as primidone. When either acetazolamide or primidone was added to phenobarbitone in mixed epilepsy, the acetazolamide was the more effective drug in one case and of equal value in another.

Side-Effects.—Five of the 26 patients complained of paraesthesia of the hands and feet, which usually persisted for about one week and recurred with an increase of dose. Excessive drowsiness occurred in four and amphetamine had to be given; all of these patients had doses greater than 8 mg. per kg. One patient became depressed and irritable, but, on the other hand, behaviour difficulties decreased in three children, and "socialization" was reported by their parents. This latter effect has also been observed by P. K. Robinson (1955, personal communication).

Discussion

The majority of our cases were of the idiopathic type of epilepsy and each variety has been carefully considered. The small number of cases has prevented a determination of the percentage control of seizures as employed by other authors, but a grading of the effects of the drug may be used as a crude indication of its value. It is realized that complete remissions are a feature of untreated idiopathic epilepsy, and that in 3.5% of cases these may be two years or more in duration (Turner, 1903). Thus evaluation of a new therapy over a shorter period is dangerous. With both these points in mind we feel that our results indicate acetazolamide to be of some value as an anticonvulsant agent, either alone in major and minimal epilepsy or as an adjuvant in some cases of the mixed type. No patient has been made worse and side-effects were few and invariably mild.

Bergstrom *et al.* (1952) reported less encouraging results with acetazolamide in 42 subjects suffering from intractable epilepsy and thought that it was of very limited use in the management of that condition. However, Munoz and Gomensoro (to be published) found it to be effective as complementary therapy in many of their patients, but the type of case in which it was employed is not known. Further support has been given by Lombroso *et al.* (1956) and Ferroni *et al.* (1955). The patients treated by Merlis (1954) had associated psychiatric disorders, and again assessment is not easy, although this author also described the beneficial effect of acetazolamide in many cases. No serious side-effects have been reported by any workers.

The dose used at the onset of this investigation was small compared with that of other authors (Merlis, 1954). However, 125 mg. twice daily having been shown to have an adequate pharmacological effect in the form of a systemic acidosis (Counihan *et al.*, 1954), it was decided to begin with this. In some cases in which the small dose was ineffective initially, a larger one was of value. Thus it soon became clear that the clinical response to acetazolamide diminished in many cases but usually returned with an increase in the dosage, and that the dosage should be

increased to the tolerance of the patient. The improvement following an increase in dosage, once unresponsiveness has developed, does not often take place with other anticonvulsants, and because of the infrequency of toxic reactions to acetazolamide a large amount can be administered with safety. Eight of the patients we studied, however, all of whom showed a most satisfactory response and then returned to their previous state in about two months, did not improve when the dosage was increased to as much as 20 mg. per kg.

The observation of Lombroso *et al.* (1956) and of Merlis (1954), that patients showing enhancement of their E.E.G. abnormalities with overbreathing are more likely to respond to acetazolamide, was not confirmed in this study. Neither were we able to correlate the clinical response with improvement in the E.E.G., although the danger of drawing conclusions from a small number of records on individual patients in this respect is appreciated.

The mode of action of acetazolamide in epilepsy is as yet unknown, but when considering it as a therapeutic agent in this condition the production of a systemic acidosis was anticipated as its major role, although the plasma bicarbonate in epileptics is normal (Lennox, 1928). However, our results do not support this view, for some of our patients with only slight changes in their bicarbonate levels had an excellent result, while in others with a profound acidosis the drug was ineffective. Also, some of the patients who developed resistance to it did so while the bicarbonate level was below 20 mEq/l. This is in accordance with the findings of Bergstrom *et al.* (1952), who maintained a low serum bicarbonate with no effect in one child with petit mal, and also with those of P. K. Robinson. Counihan *et al.* (1954) have shown that with continued administration bicarbonate excretion drops to zero and the electrolyte pattern of the blood returns to the control state.

The relationship of epilepsy to body-fluid disturbance is well established (Gamble, 1930). Excessive ingestion of water may produce fits, while restriction can reduce both the actual number of attacks and the abnormal appearances of the E.E.G. (Hatfield *et al.*, 1954). Thus it seemed feasible that dehydration resulting from the diuresis that accompanies the administration of acetazolamide might play a part. However, this diuresis is short-lived because it depends on an increase in bicarbonate excretion and thus, by the production of a systemic acidosis, becomes self-limiting. As the diuresis lasts only hours at the maximum, it cannot explain even the temporary improvement which occurred in some of our cases. In three subjects the total body water was estimated by the antipyrine method (Soberman *et al.*, 1949) while the subject was without treatment and repeated while being maintained on an established dose of acetazolamide with a clinical grading of excellent. There was no significant change, thus giving further support to the conclusion that dehydration does not play a part.

Using ion-exchange resins in epileptics, Klingman (1954) found that it was possible to produce clinical improvement and to reduce the E.E.G. abnormalities by reducing sodium; and in one case, by removing potassium, he demonstrated a focus in the E.E.G. He suggested that the improvement on removing sodium resulted from acidosis, dehydration, and neuronal sodium reduction. He found no change in the serum sodium. The excitability of the central nervous system as measured by electric-shock seizure is inversely proportional to the sodium in the extracellular fluid (Mitchell and Ogden, 1954). Other work (Tower, 1955) shows that the epileptic brain cells seem less able to expel sodium than the normal. Acetazolamide is capable of causing a greatly increased excretion of sodium, but, as with water, this is not maintained. It may, however, be that part of its action is by modification of the electrolyte composition of the extracellular fluid and cells. In one patient, in whom sodium metabolism was observed closely, the serum levels taken at weekly intervals over a four-months period showed no change from before treatment. As an anti-epileptic agent acetazolamide was effective only in the first two months. Throughout the period the patient was on treatment the serum potassium (3.6 mEq/l.) was slightly below the pre-treatment level (4.2 mEq/l.).

It is doubtful whether an electrolyte imbalance plays a part in the epileptic, except perhaps at the menses, when sodium and water are retained in excess and seizures are known to be more common (J. Laidlaw, 1955, personal communication). Continuous administration of acetazolamide, however, is unlikely to have much influence on this. In three patients and one healthy subject it only slightly modified their usual pre-menstrual gain in weight. However, when introduced immediately before the menstrual period in the healthy subject it caused a marked sodium-and-water diuresis. Thus in a further two subjects—not included in this trial—suffering from major idiopathic epilepsy, who showed marked menstrual aggravation of their seizures and who had regular cycles, acetazolamide was given on the day before the first day of the period and the day immediately after, in a dosage of 5 mg. per kg. daily, with marked benefit over three cycles—a benefit presumably due to its diuretic effect.

Finally, it is possible that the beneficial effect of acetazolamide is in part due to a direct action of the drug on carbonic anhydrase in the brain, despite the fact that Bergstrom *et al.* (1952) found no correlation between clinical events and the level of this enzyme in the blood of epileptics. Ashby (1944) has shown that the amount of carbonic anhydrase varies in different parts of the brain, and that in humans there tends to be more in the thalamus than in the cerebral cortex. It is related to cerebral activity (Ashby, 1954) and there seems to be a synchronization of its onset with the appearance of the enzyme (Ashby and Schuster, 1950). In addition, it is reasonable to suppose that it may play a part in epilepsy. Thus Ashby (1950) found that in a series of brains a specific abnormality of the enzyme occurred only in two epileptics whose seizures had been inadequately controlled, and Ferroni *et al.* (1955) report a correlation between the enzyme and E.E.G. activity. This conception of the action of acetazolamide in epilepsy seems the most reasonable, but as yet little is known about the epileptic brain and its carbonic anhydrase content, and the effect of carbonic anhydrase inhibitors upon it.

It is possible that this drug is effective by virtue of more than one of its actions, but, in any case, it will no doubt prove to be a useful agent for the further investigation of cerebral physiology and the mechanism of epilepsy. Variable response amongst otherwise similar clinical varieties of epilepsy suggests that the group now classed as idiopathic is not homogenous.

Summary

Acetazolamide ("diamox") may be of value as the sole therapeutic agent in the treatment of major epilepsy of moderate severity, in some cases of minimal epilepsy, and as adjuvant therapy in mixed idiopathic epilepsy.

Repeated increase of dosage is often necessary, but as the drug is relatively non-toxic it can be used in doses up to 20 mg. per kg. of body weight.

Its mode of action is unknown. In continued dosage it does not appear to depend upon the production of a systemic acidosis, or on its diuretic effect. Given at the time of the menses, its beneficial influence in some epileptics may, however, be related to the diuresis. A suggestion is made that it may act specifically on the carbonic anhydrase in the epileptic brain.

ADDENDUM.—Since the completion of this article Millichap, Woodbury, and Goodman (*J. Pharmacol.*, 1955, **115**, 251) have shown experimentally in mice that acetazolamide acts as an anticonvulsant by direct inhibition of carbonic anhydrase in the brain. Further observations on its biochemical (Ferroni, Lipani, and Catanzaro, *Acta neurol.*

(*Napoli*), 1955, **10**, 722; Lipani, ibid., 1955, **10**, 815) and electroencephalographic (Ferroni and Gattuso, *Acta neurol. (Napoli)*, 1955, **10**, 832) effects in epileptics as well as a survey of the subject (Annotation, *Lancet*, 1956, **1**, 273) have also been published.

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TREATMENT OF CONTACT DERMATITIS DUE TO HANDLING ANTIBIOTICS

BY

R. M. MORRIS-OWEN, B.M., B.Ch.

Registrar, Allergy Clinic, Radcliffe Infirmary, Oxford

The widespread use of penicillin and streptomycin has created a new occupational hazard for doctors and nurses. While most can handle these substances without difficulty, a few develop allergic reaction to skin contact with them and may thereby suffer considerable disability. A number of workers have treated such cases by "desensitization," using the classical method of injecting steadily rising doses of the specific sensitizing agent (Cohen and Glinsky, 1951; Crofton, 1953; Russell, 1953; Wheeler, 1953; O'Brien, 1954; Binns, 1955; O'Driscoll, 1955).

This paper describes a method of treatment in which injections of the specific agent are used on a different principle. This arose from the observation that patients receiving minute doses in the first phase of a classical desensitization were immediately much less vulnerable to contact. This transient tolerance to contact can be maintained by frequent repetition of the same small dose. In certain patients, when symptoms of reaction have in this way been held in complete suppression throughout a sufficient period of constant handling, tolerance to contact has persisted after stopping the treatment.

The method is simple and may be used in either of two ways. For the patient who has to incur regular exposure, constant treatment is maintained until a trial relaxation shows tolerance to be stable. For a patient who is less often exposed to contact it has been sufficient to give such treatment as is required to cover each separate occasion, although stable tolerance is less readily set up by such occasional treatment.

Solutions of benzylpenicillin (crystalline penicillin G) and streptomycin sulphate in normal saline have been used throughout. Solutions for testing have always been freshly prepared. For patients taking regular treatment it has been usual to replace them fortnightly, with a dosage adjustment to compensate for deterioration, which has been checked by frequent assays.

Diagnostic Methods

In nearly all these cases the history is decisive, but epicutaneous tests are useful for confirmation and to exclude other allergies. Subcutaneous testing is an alternative method of confirming contact sensitivity to an antibiotic, and is the only method to give quantitative guidance for treatment.

Epicutaneous testing is usually done by the closed-patch technique, for which in the present work a half-inch (1.3-cm.) square of lint wetted with a solution of appropriate strength has been applied to the outer surface of the arm under a one-inch (2.5-cm.) square of "cellophane," secured by adhesive plaster. Positive reaction to this test is often associated with flare-up of remote areas, especially those previously involved in clinical reaction. In some cases such remote reaction is the only result of a patch test. A "drop technique" has also been used in this work, placing drops of solution in contact with the volar surface of the forearm for 20 minutes and then washing thoroughly. In cases of occupational antibiotic sensitization this produces the local eczematous reaction as effectively as patch-testing and provokes much less remote reaction. It is therefore to be preferred as a routine test.

Subcutaneous Testing.—Systemic administration of a drug to which the patient has a skin-contact sensitization may provoke either a generalized dermatitis or a flare-up of sites of previous clinical reaction, resembling the remote reaction to the patch test. Cautious use of this method of provocation has the same diagnostic value as a patch test, together with the advantages of more exactly quantitative results and of provoking earlier and less protracted reaction.

Case 1

In April, 1954, a general practitioner was considering giving up clinical work on account of his sensitivity to penicillin. For two years he had had severe cutaneous reactions of the face and neck every time he handled the drug, and sometimes had had reactions from examining patients under treatment with it.

A subcutaneous test with ¼ unit of penicillin was followed in a few hours by a mild reaction on the face. A week after this had subsided he took 1/10 unit without reaction. He went on cautiously increasing the subcutaneous dose, and three weeks later could take 3 units. He then gave one injection of penicillin to a patient and at the same time deliberately sprayed some of the solution on to his own fingers. Patches of mild papular eruption appeared on his hand and face some hours later, but the reaction was trivial in comparison with his earlier ones. His dose was then gradually increased to 5 units daily and maintained at this level for three months, during which time he gave many further penicillin injections to patients without suffering any further reactions.

In September the strength of his solution had been allowed to run down in order to bring about a trial tapering of the