counts expected, if 100% of the injected ^{51}Cr -labelled red cells survived, could be predicted. A sample taken eight minutes after injection contained 99% of the expected number of ^{51}Cr -labelled cells; a sample taken 33 minutes after injection contained only 91%, while a sample taken at three hours contained 55%. A sample taken 22 hours after injection contained only 1% of cells (see Chart). The amount of radioactivity in the plasma was measured in all samples, and the largest amount (representing 6.7% of the total ^{51}Cr injected) was found in the three-hour sample.

On June 24 a sample of the patient's own cells was labelled with ^{51}Cr and reinjected to estimate the average life-span of the patient's own cells in her own circulation. The ^{51}Cr -labelled cells were removed relatively slowly, and the average life-span was estimated to be 11 days (see Chart).

Serological Findings

The patient's full blood groups were determined by Dr. D. Parkin, of the Blood Groups Research Unit of the Lister Institute, as follows: O, CcDE, N, S-, P+, Lu(a-b+), K-, k+, Le(a+b-), Fy(a+), Jk(a+b-), Vel+, Yt(a+).

The donor, whose red cells were labelled with ^{51}Cr , had the following blood groups: O, cddEe, M, S-, P+, Lu(a-), K-, Le(a+b-), Fy(a+). Cells of this donor were tested with the patient's serum before they were injected, and were tested again on two subsequent occasions. No reaction of any kind could be demonstrated using the following tests: agglutination in saline; agglutination in albumin; agglutination of enzyme-treated cells; indirect antiglobulin (Coombs) test against untreated cells; and indirect antiglobulin test against enzyme-treated cells. In case the serum was anticomplementary, the indirect antiglobulin test was carried out in two stages, the cells being first incubated with the patient's serum, then washed and resuspended in fresh serum from a normal donor before being finally washed and tested with the antiglobulin serum.

Haemolysis could not be demonstrated with any of these tests, either when human serum or when rabbit serum was used as a source of complement. (For the possible advantages of using rabbit serum as a source of complement in detecting human blood group antibodies, see P. L. Mollison and Ann R. Thomas, 1959, to be published.) The patient's serum was also tested by Dr. Parkin, who reported that no blood-group antibodies could be found using a series of tests, including the "trypsin-Coombs" test.

Discussion

When transfused red cells undergo complete destruction within 24 hours it is to be expected that an antibody, incompatible with the donor's red cells, will be found in the patient's serum. Fudenberg and Allen (1957) have described some cases in which transfused red cells were rapidly destroyed, with haemoglobinuria in one instance, even though no antibody was demonstrable at the time of transfusion. However, in all these cases antibody was either demonstrated some days after transfusion or was known to have been present some time before transfusion.

A diminished survival of transfused red cells due almost certainly to incompatibility but without demonstrable antibody is now well recognized (Loutit, Mollison, and Young, 1943; Mollison, 1956; Jandl and Greenberg, 1957; Adner and Sjölin, 1957), but in these cases the elimination of the donor's red cells takes some days or weeks.

The present case is remarkable in that such rapid destruction occurred in the absence of a demonstrable antibody.

Summary

A case is described in which the patient repeatedly suffered severe haemolytic reactions after the transfusion

of apparently compatible blood. It was demonstrated that the transfused red cells were completely eliminated from the circulation within 24 hours of the transfusion, but all known tests for blood-group antibodies failed to reveal any incompatibility *in vitro*.

We thank Mrs. Crookston (formerly Miss Marie Cutbush) for carrying out most of the serological tests; Dr. Dorothy Parkin for determining the full blood groups of the patient and of one of the donors; and Miss M. D. Snelling for permission to publish clinical details of this case.

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BECLAMIDE IN INTRACTABLE EPILEPSY: A CONTROLLED TRIAL

BY

JOHN WILSON, M.B., B.Sc., M.R.C.P.

Late Senior House Officer

JOHN N. WALTON, M.D., M.R.C.P.

Assistant Physician

Neurological Unit, Department of Medicine, Royal
Victoria Infirmary, Newcastle upon Tyne

AND

D. J. NEWELL, M.A.

Statistician, Nuffield Department of Industrial Health,
King's College, University of Durham

Though several powerful anticonvulsants have served to transform the management of patients suffering from major epilepsy, there remain a number of epileptics whose attacks are poorly controlled. In such a group of cases attending an epileptic clinic in Newcastle upon Tyne we decided to try the effect of beclamide ("nydrane"; "hibicon"; N-benzyl-B-chloropropionamide). This promising drug is structurally quite different from the conventional anticonvulsants, and has the additional advantage of being relatively non-toxic in therapeutic doses. Its exact mode of action has not yet been determined.

Several favourable reports have already appeared (Hawkes, 1952; Hoenig *et al.*, 1956; Merlis and Martin, 1956; Robinson, 1957; Sharpe, Dutton, and Mirrey, 1958), and we wish to record here our experiences of a double-blind controlled trial using this remedy.

Clinical Material and Methods

Among the patients attending the epileptic clinic of the Royal Victoria Infirmary at the beginning of the proposed trial (September, 1957) were 16 whose attacks were clearly uncontrolled despite substantial doses of the commoner anticonvulsants in many different combinations. Three of these patients were deemed unsuitable for the trial: the first was pregnant, the second was a psychopathic adolescent girl who was subsequently admitted to a mental hospital, and the third was a mentally defective woman of 34 whose

TABLE I.—*Clinical Details of the Patients in the Trial*

Case No.	Age	Clinical Type of Epilepsy	E.E.G. Findings	Age of Onset (Yrs)	Anticonvulsant Remedies Previously Received					
					PB.	MPB.	Prim.	Acet.	Ph.	Me.
1	44	Post-traumatic	Not done	39	PB.	MPB.	Prim.	—	Ph.	—
2	27	Focal	Temporal lobe spikes	17	"	"	"	—	"	—
3	38	? Temporal lobe	Normal	27	"	"	"	—	"	—
4	34	Grand mal	Not done	18	"	—	"	—	"	—
5	49	"	"	46	"	—	"	—	"	—
6	45	"	Normal	43	"	—	"	—	"	—
7	21	Structural with birth injury	Temporal lobe spikes	11	"	—	Prim.	Acet.	"	—
8	39	? Temporal lobe	Synchronous spike and wave	6	"	—	"	—	"	—
9	21	Focal	Parieto-temporal delta activity	10	"	—	"	—	"	—
10	51	Grand mal	Temporal lobe delta activity	43	"	—	"	—	"	—
11	30	Temporal lobe	Temporal lobe spikes	13	"	—	"	Acet.	"	Me.
12	50	"	"	41	"	MPB.	—	—	"	"
13	38	"	Normal	12	"	—	Prim.	—	"	—

PB.=Phenobarbitone. MPB.=Methylphenobarbitone. Prim.=Primidone. Acet.=Acetazolamide. Ph.=Phenytoin. Me.=Methoin.

relatives were unreliable. The diagnosis of major or temporal lobe epilepsy in the remaining 13 cases was clearly established on clinical grounds, and confirmatory electroencephalographic evidence was available in the majority of cases. Table I gives brief clinical details of the cases and of the previous treatment they had received. Most of these patients were living active and useful lives despite their attacks, and all attended hospital at monthly intervals for review throughout the trial.

At the outset the purpose of the trial was explained, and each patient agreed to co-operate fully. The anticonvulsants which the patients had been taking immediately before the trial period began were continued throughout. The patients (or responsible relatives) were asked to keep an accurate record of the date and time of epileptic seizures and to note possible side-effects of treatment. All patients were seen and examined at monthly intervals by one of us (J.W.), special attention being paid to the skin, lymph nodes, gums, signs of ataxia, and reflex changes. At the end of each monthly period the patients were questioned about the number of tablets which were left, since from this it was possible to judge whether the medication had been taken regularly. Haematological studies (Hb, W.B.C., differential white count) and urinalysis were carried out at the beginning of the trial, and at each three-monthly stage thereafter.

For a preliminary period of three months the patients were observed on the anticonvulsant regimen they were already taking. During each of the two subsequent three-monthly periods they received either unmarked beclamide tablets in a dosage of 1 g. three times daily or else identical control tablets of lactose, in addition to the drugs they were already receiving. Care was taken to see that the tablets were taken routinely each day at the same times. Neither the patients nor the doctor responsible for assessing the results (J.W.) knew which tablet was being taken at any one time. Tablets were packaged in the hospital dispensary and were administered according to a prearranged plan devised by one of us (D.J.N.).

At the end of this six-monthly period those patients whose attacks were still relatively uncontrolled were observed for a further four to eight weeks while receiving beclamide in a dosage of 4 g. daily in addition to their previous medication.

Results

The two major difficulties encountered in this outpatient trial were (1) maintaining accurate records of attack frequency; and (2) ensuring that patients took

their tablets regularly. Judging by the numbers of tablets left at the end of each month it is certain that most patients took the full dose of tablets, whilst the others took at least 90% of the recommended dose. Both difficulties are overcome to a certain extent, however, by conducting a controlled trial, since these imponderables were obviously operating during both test and control periods. We feel, therefore, that the numbers of seizures per patient in each period of the trial as recorded in Table II are reliable for our purpose.

TABLE II.—*Results of Controlled Trial, Showing Numbers of Seizures Occurring During Each Treatment Period*

Case No.	Existing Treatment (Daily Total)	No. of Seizures During Each Period of Trial			
		I	II	III	IV
1	Primidone 1½ g., phenytoin 4½ gr. (0.3 g.)	15	14 C	18 + B	4 (4 wks)
2	Primidone 1 g., phenytoin 4½ gr. (0.3 g.), acetaz. 500 mg.	237 +	296 + C	153 + B	53 + (4 ..)
3	Primidone 1 g., phenytoin 6 gr. (0.4 g.)	16	11 B	12 C	1 (4 ..)
4	Phenobarb. 1½ gr., phenytoin 6 gr. (0.4 g.)	15	5 C	2 B	0 (8 ..)
5	Primidone 1½ g., phenytoin 4½ gr. (0.3 g.)	45	45 B	29 C	21 (9 ..)
6	Phenobarb. 1½ gr., phenytoin 3 gr. (0.2 g.)	5	7 C	7 B	9 (9 ..)
7	Primidone 1½ g., acetaz. 500 mg., Phenytoin, 3 gr. (0.2 g.)	95 +	59 + B	120 + C	32 (4 ..)
8	Primidone 1½ g., phenytoin 4½ gr. (0.3 g.)	9	0 B	0 C	1 (4 ..)
9	Primidone 1 g., phenytoin, 1½ gr. (0.1 g.)	152	107 B	119 C	29 (4 ..)
10	Phenobarbitone 1 gr., phenytoin 3 gr. (0.2 g.)	6	3 B	8 C	6 (9 ..)
11	Methoin 300 mg., phenobarb. 3 gr., phenytoin 4½ gr. (0.3 g.)	31	35 C	23 B	14 (8 ..)
12	Methoin, 200 mg., methylphenob. 3 gr., phenytoin 3 gr. (0.2 g.)	33	11 C	12 B	—
13	Primidone 750 mg., phenytoin 3 gr. (0.2 g.)	5	8 C	3 B	—

Period I= Preliminary three months observation period. Period II= First three months of controlled trial: 3 g. day of beclamide or lactose in divided doses. Period III= Second three months of controlled trial: 3 g./day of beclamide or lactose in divided doses. Period IV= Further period (stated): 4 g./day in divided doses. B=Beclamide. C=Control.

Clearly there is a great deal of variability in the results, and in some of the patients who had large numbers of fits it was impossible to obtain an accurate figure.

In these circumstances the method of transforming the observations into *log* (number of fits + 1) was used to produce normal variables to which standard statistical tests can be applied (Quenouille, 1950). There is some justification for using a logarithmic transformation of the number of fits, in so far as a successful treatment might be expected to reduce the number of fits by a constant *proportion*—for example, to half the number suffered without the treatment—rather than by a constant *number* of fits per three-monthly period. Thus a

constant change in the logarithm of the number of fits is the desired effect of a treatment. The addition of 1 to the number of fits before taking logarithms is necessitated by the fact that in a few patients 0 fits were recorded in a period. In this section of the report, *log* (number of fits + 1) in a particular period and for a particular patient is referred to as the score.

Comparison of Beclamide with the Control (Periods II and III)

The effect of beclamide in each patient was measured by subtracting the score for the control from the score for beclamide. In the 13 patients these varied from +0.18 to -0.35, with an average of -0.118. This figure is significantly different from zero ($t=2.32$, $d.f.=12$, $P<0.05$). Translating back from logarithms, this means that beclamide reduces fits to about 75% of the figure with the control tablets. When on beclamide three of the patients had more attacks, two had the same number, and eight had fewer.

The 13 patients were divided as equally as possible into groups receiving beclamide in the second period and in the third period, there being six in the first group and seven in the second. Allocation to these groups was made by random selection before the trial began.

The second and third periods coincided with the snowy winter of 1957-8 and the wet spring of 1958. To investigate the possible effect of season on the frequency of seizures a comparison of the scores in the second and third periods (regardless of the treatment given) was made. The average difference between scores was only 0.033, which is not significant ($t=0.55$, $d.f.=12$, $P=0.60$).

Effect of the "Control" Tablet

Having thus established that there was no intrinsic difference between the second and third consecutive periods themselves, we were able to compare the scores in these periods with those in the first (observation) period. Comparison of the results in the first period with the same patient's control period in the second or the third period shows that seven patients had fewer fits with the control tablets than with no additional tablet, but the other six had more fits. Thus there is no significant difference between the dummy tablets and observation, and possible psychological effects of an inert tablet can be discounted in this trial. (Comparison of scores between first and control periods yields the same result: $t=1.40$, $d.f.=12$, $P=0.20$ —not significant).

Effect of Increased Dosage of Beclamide

The effect of increasing the dosage of beclamide to 4 g. a day was tested more briefly in 11 patients at the end of the third period. While it is not recommended that a further period should be added to a balanced design, we feel that the similarity between results in the second and third periods to some extent justifies comparisons between the results in this fourth period and those in previous ones. The shorter periods used make the test rather less sensitive than those in the main part of the trial.

For comparison, the numbers of fits recorded in four, eight, or nine weeks were increased proportionately to give the corresponding figures for 12 weeks (as in periods II and III). Six of the 11 patients had proportionately more fits than in the period in which they were receiving beclamide in the dosage of 3 g. a day. The average difference between the scores was only 0.01, giving no evidence at all in favour of the higher dosage. However,

the variability in results was greater, and the 95% confidence limits for the average difference in scores are from -0.21 to +0.19, meaning that the higher dosage could in the long run reduce fits to 60% or increase them to 162% within the limits of the data here recorded.

Side-effects

Several patients attributed occasional nausea and anorexia to the tablets, but these symptoms can be discounted because they occurred just as often with the supposedly inert controls. The size of the tablets (0.5 g.) caused difficulty in a minority of patients. The drug was never incriminated as a cause of skin rash, gum hypertrophy, or any neurological abnormalities. Depression or somnolence was not observed as an indubitable effect of the tablets; neither was a specific euphoriant effect detected, apart from the optimism arising from better control of seizures in certain patients.

Four patients developed a mild hypochromic anaemia over the course of the whole trial period, but we were able to attribute this in all cases to blood loss (haemorrhoids, menstruation, etc.) or to poor diet. One patient (Case 7) developed a severe macrocytic anaemia (Hb, 8.25 g. per 100 ml.) which responded rapidly and completely to oral folic acid; he was already having large doses of phenytoin and primidone, and it seems probable that these drugs and not the beclamide were responsible for the anaemia.

Albuminuria and reducing substances in the urine were not detected in any case.

Discussion

As in trials previously reported, beclamide was found to exert a significant though not strikingly beneficial effect when given in divided doses of 3-4 g. a day in poorly controlled epileptics. Nine out of 13 patients were improved, with a reduction in the overall frequency of seizures to 75% of the previous figure. Our observation did not suggest any difference in the efficiency of the drug in apparent "idiopathic" epilepsy on the one hand, or in focal or temporal lobe epilepsy on the other. We did not use this remedy in cases of petit mal. Compared weight for weight with the commonly used anticonvulsants, beclamide is not a powerful agent, but it has the singularly valuable property of being non-toxic in therapeutic doses. Our observations tend to confirm the non-toxicity of the drug, though it must be emphasized that a longer trial than ours would be necessary to exclude toxic effects.

Initial leucopenia and the transient appearance of a reducing agent in the urine have been reported by other workers, but these changes were never observed in our cases, possibly because haematological studies and urinalysis were carried out only at three-monthly intervals.

We believe that beclamide has a place in the management of major or temporal lobe epilepsy, but its relative lack of efficiency as an anticonvulsant, together with the large size of the tablets, which makes them unsuitable for children, as well as their price (currently £18 per 1,000 tablets, compared with £6 4s. per 1,000 tablets for primidone, the most expensive of the anti-convulsants in common use), will limit the use of this drug to epileptics whose fits are poorly controlled by phenobarbitone, phenytoin, or primidone, or for whom these drugs are too toxic.

Summary

In a statistically controlled double-blind trial of beclamide in 13 patients suffering from uncontrolled major or temporal lobe epilepsy it was shown that that drug, in a dosage of 3 g. daily, was significantly more efficient than an inert tablet, reducing the number of seizures to 75% of their previous frequency without any noteworthy side-effects. Control (inert) tablets were shown not to have any psychological placebo effect. Little improvement occurred on increasing the dosage of beclamide from 3 g. to 4 g. a day, but this increased dosage was given for a relatively short period and the evidence on this point is inconclusive.

It is concluded that beclamide has a significant anti-convulsant effect, but in view of the high cost of this remedy it should be used only in epileptic patients who have failed to respond to other remedies. It appears that the drug may safely be given in combination with other anticonvulsants.

We thank Dr. H. G. Miller for allowing us to include in the trial patients who were under his care; Miss Garnett, chief pharmacist, Royal Victorial Infirmary, for her co-operation in arranging the double-blind controlled trial; and Dr. S. Phillips and Rona Laboratories Ltd. for supplying the beclamide and identical control tablets.

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RENAL FAILURE IN HYPERCALCAEMIC SARCROIDOSIS

BY

D. J. DELLER, M.B., M.R.A.C.P.

Medical Registrar

I. A. BRODZIAK, M.B., F.R.A.C.P., M.R.C.P.

Honorary Physician

AND

ALLISON D. PHILLIPS, M.B., B.S.

Resident Medical Officer

The Royal North Shore Hospital of Sydney

Hypercalcaemic sarcoidosis is associated in many cases with renal failure. Sarcoid granulomatous infiltration of the kidneys is not uncommon, but the lesion is usually focal and not extensive. Berger and Relman (1955) reported a case of sarcoidosis and renal insufficiency showing granulomatous infiltration of the kidneys without nephrocalcinosis or associated renal disease. Other diseases, such as pyelonephritis (Dent *et al.*, 1953) and renal tuberculosis (Longcope and Freiman, 1952), may be present to account for renal insufficiency in patients with disseminated sarcoidosis. Klatzkin and Gordon (1953) suggested that renal failure in sarcoidosis may be due to hypercalcaemia and nephrocalcinosis. The association of nephrocalcinosis and renal failure in hypercalcaemic sarcoidosis has been reported (Longcope and Freiman, 1952; Shulman *et al.*, 1952; Davidson *et al.*, 1954; Scholz and Keating, 1956). In addition, steroid therapy has been followed by reduction of the hypercalcaemia and improvement in renal

function (Shulman *et al.*, 1952; Dent *et al.*, 1953; Gleckler, 1956; Phillips and Fitzpatrick, 1956; Scholz *et al.*, 1957). We report a case of hypercalcaemic sarcoidosis with renal failure. Steroid therapy resulted in improvement in renal function, although serial renal biopsies showed persistence of nephrocalcinosis.

Case Report

A 36-year-old man was admitted to hospital on April 21, 1958. He complained of weakness, polyuria, polydipsia, insomnia, and exertional dyspnoea, gradually increasing over two years. The past medical history revealed that in 1947 he developed a polyarthritis which responded poorly to salicylates. In 1953 a pulmonary lesion was detected by x-ray examination, and on the basis of follow-up radiological and sputum studies a diagnosis of sarcoidosis was made. He had no history of excessive intake of milk, alkalis, or vitamin D.

The physical examination revealed an asthenic, sallow man. There were no skin lesions. Band keratitis was absent. The blood pressure was 140/90 mm. Hg; pulse rate 80 a minute; temperature 98.6° F. (37° C.); respirations 22 a minute. There was enlargement of the spleen to 4 cm. below the left costal margin.

Laboratory examination showed a blood haemoglobin of 10.5 g./100 ml., and white-cell count of 5,000/c.mm., with a normal cell distribution. The sedimentation rate was 20 mm./hour (normal 2-6 mm./hour). Red-cell indices showed a normochromic normocytic anaemia, and the direct Coombs test was negative. The specific gravity of the urine was 1.010 and the daily urine volumes averaged 2,800 ml. Water deprivation did not correct the isosthenuric polyuria. There was no proteinuria, cylinduria, haematuria, or pyuria. Urine was sterile on culture. Mantoux reaction 1:1,000 was negative. X-ray examination of the chest revealed diffuse fibrosis scattered throughout both pulmonary fields. X-ray studies of the hands, feet, and spine showed no abnormality. A plain x-ray film of the abdomen disclosed a small calculus in the lower pole of the right kidney. An intravenous pyelogram showed poor dye excretion by both kidneys. Renal tomography did not demonstrate calcinosis. The kidneys appeared normal in size and position. An electrocardiogram was normal. The blood urea was 93 mg./100 ml. Serum calcium was 13.2 mg./100 ml.; serum phosphorus, 4 mg./100 ml.; serum alkaline phosphatase, 8 King-Armstrong units; total protein, 7.7 g./100 ml. (serum albumin 4.3 g., serum globulin 3.4 g.); electrophoretic pattern showed an increase in gamma-globulin; serum bilirubin, 0.2 mg./100 ml.; thymol turbidity, 0.5 unit; zinc sulphate, 5.8 units; blood cholesterol, 58 mg./100 ml.

A left aspiration renal biopsy (Fig. 1) was performed by one of us (D.J.D.) with a Franklin modification of the

FIG. 1.—Renal biopsy before commencement of cortisone. Nephrocalcinosis with increase in interstitial connective tissue and cellular infiltration. (Haematoxylin and eosin. $\times 103$.)