altered circulatory state only at the expense of a considerable rise in left atrial and subsequently pulmonary capillary-venous pressure. Hence, pulmonary oedema during pregnancy is a not uncommon event. As previously noted, Morgan Jones (1951) found pulmonary oedema to be the most important cardiac cause of death in pregnancy.

In four of our cases (Nos. 13, 14, 16, and 18) the stenosis was only moderate, the valve orifice admitting the index finger to the proximal interphalangeal joint. Nevertheless, these women presented with pulmonary congestion or oedema which persisted or recurred despite treatment with salt-free diets, complete bed rest, and mercurial diuretics. In one of the patients in whom cardiac catheterization was performed the resting pulmonary "capillary" pressure was still 29 mm. Hg after two weeks' such treatment. It is clear that moderate stenosis in the presence of the raised cardiac output and hypervolaemia of pregnancy can produce the same effects as tight stenosis in the non-pregnant patients, and that pre-operative assessment of the size of the valve orifice in many cases is a matter of great difficulty.

Opinions are still divided concerning the indications for mitral valvotomy in pregnancy. Burwell and Metcalfe (1954) state that surgery of the mitral valve should be avoided if at all possible and that the operation should be carried out only when "the safer procedure of interruption is not practicable." It is their opinion that most women who undergo valvotomy during pregnancy "would probably do well without an operation if the medical supervision was adequate" and that the operation is more hazardous during pregnancy.

It is true that pulmonary congestion and mild pulmonary oedema occurring in pregnant women with mitral stenosis are often easily controlled by medical means. However, in the cases reported here several of the patients were admitted *in extremis* and remained so despite therapy. The others showed pulmonary congestion or oedema uncontrolled by a fair trial of medical measures. It is apparent that patients in this state demand valvotomy. This is particularly so since the experience recorded here indicates that the operative risk is no greater during pregnancy than in the non-pregnant state.

In two patients (Cases 1 and 3) the operation was apparently the cause of premature labour at the 34th and 32nd weeks; one of these infants failed to survive. The remaining pregnancies, however, continued without incident. Since valvotomy was undertaken at the 18th week or later in all but three cases, it might be held that the incidence of post-operative abortion would be higher for operations performed earlier in pregnancy. However, all seven cases reported by Watt *et al.* (1954) had their operations between the second and fifth months of pregnancy; in none of these was there "any hint of threatened abortion." Several authors (Glover *et al.*, 1955; Bailey and Bolton, 1956) recommend that when surgery is likely to be required it should be undertaken as early as possible in pregnancy.

Summary

Mitral stenosis is an important cause of morbidity and mortality during pregnancy. The principal hazard is pulmonary oedema, which may develop with dramatic suddenness. Moderate mitral stenosis during pregnancy may produce the same effects as tight stenosis in the non-pregnant patient.

In the past six years 18 patients have undergone mitral valvotomy during pregnancy. The indications for the operation and the results are reported. The operation was undertaken in some as an emergency and in the remainder after a fair trial of medical treatment. There was no maternal death or any important post-operative complication. One foetus, born prematurely, failed to survive.

In suitably selected cases mitral valvotomy is preferable to termination of pregnancy.

We are indebted for the co-operation of Mr. T. B. Smiley, who performed valvotomy in 14 of the cases, and that of Mr. J. A. W. Bingham, who performed the operation in four cases.

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NYDRANE IN THE TREATMENT OF EPILEPSY

BY

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Epilepsy is a disease which presents a continual challenge to the skill of the physician. He has waged war against this disease throughout the centuries, using whatever therapeutic weapons were at his disposal and influenced by the prejudice and state of knowledge of his era. Epileptics were subjected to treatment which embraced the whole gamut of empirical medicine. They were exorcised for devils, blistered, and bled according to the prevailing fashion.

Many remedies were tried and discarded, such as borax, amylene hydrate, zinc, chlorbutol, urethane, simulo, hydrotherapy, and serotherapy. The first measure of any importance was the introduction of bromides by Laycock just over a century ago. These drugs were applied with such enthusiasm during the ensuing years that Spratling (1904) mentions bromide acne as being the hall-mark of the epileptic.

Modern drug therapy was ushered in in 1912 by the synthesis of phenobarbitone, a drug which has established itself firmly in the treatment of epilepsy right up to the present day. Hydantoins were introduced in 1938 and proved effective in the control of grand-mal convulsions, while drugs of the oxazolodine : dione series have been in use since 1945 in the treatment of petit mal. Biochemists in different parts of the world have been intensifying their researches recently, and their efforts have brought to light several new compounds which have been shown to possess anticonvulsant activity. This modern empiricism reminds one of the biblical admonition that "many are called, but few are chosen"; nevertheless it is to the advantage of the patient that the physician should have at his disposal as many useful drugs as possible and each new drug must be studied carefully, so that its uses and limitations may be assessed.

It was with these considerations in mind that a trial was begun of a recently introduced anticonvulsant called "nydrane." It has the chemical composition of N-benzyl- β -chloropropionamide and was originally discovered in America, where it was marketed as "hibicon." Experimental studies on laboratory animals have shown that nydrane raises the electrical threshold and

will protect them against a lethal dose of pentylene-tetrazole and artificially produced convulsions. It is a benzylamide with the formula $\text{Cl-CH}_2\text{-CH}_2\text{-CO-NH-CH}_2\text{-C}_6\text{H}_5$, and as such differs considerably from the anticonvulsants in everyday use. It is supplied in the form of tablets, each tablet containing 0.5 g.

Clinical Material

The drug was administered to 11 male patients. All were in-patients of Purdysburn Hospital, a mental hospital, and, as well as having epileptic fits of varying frequency, they suffered from an associated psychosis with some confusion, retardation, and antisocial behaviour. All were subject to convulsions of grand-mal type (idiopathic epilepsy) in spite of long-continued anticonvulsant therapy. They may be regarded as a refractory group resistant to ordinary medication and a severe test for any drug. Their ages ranged from 28 to 53, and detailed reports of their past behaviour, convulsion frequency, etc., were available for several years previously. All were under continual observation. The average number of convulsions per month to which the patients were subject varied from thirty-six to one. They were receiving phenobarbitone, phenytoin sodium, and primidone in varying dosages and combinations—for example, phenobarbitone, 1½ gr. (0.1 g.) twice daily, and phenytoin sodium, 1½ gr. (0.1 g.) twice daily, or phenobarbitone, 1½ gr. (0.1 g.), and 3 primidone tablets a day.

Before the trial started each patient was given a thorough examination, which included testing the urine and a full blood and differential white-cell count. Electroencephalograph (E.E.G.) tracings were taken of five patients.

Administration.—Initially nydrane was given in a dosage of one tablet (0.5 g.) three times a day in addition to existing medication, which was continued throughout the course of the trial in all cases. After one week this was increased to five tablets a day, and thereafter the dosage was increased by one tablet weekly until all patients were receiving seven tablets (3.5 g.) daily in divided doses. This was continued for a period of five months, after which the nydrane was gradually withdrawn. During this time a close check was kept on the blood picture, which showed minor variations, but in all cases the leucocyte count and haemoglobin were approximately the same at the end of the trial as at the beginning. There was no agranulocytosis or anaemia at any time. There was no albuminuria or sign of liver damage. The only side-effect noted was a slight gastrointestinal upset in four patients within two days of beginning treatment, but this was of short duration and did not return.

Results

In assessing results, attention was paid both to the anticonvulsant activity and to the other actions of the drug. The usual criterion on which an anticonvulsant drug is assessed is its ability to reduce or abolish convulsions, although this strictly arithmetical method does not tell the whole story. The average number of fits per month was estimated in each case for the five months preceding the trial and compared with the average number over the five months during which they received nydrane.

Average Number of Convulsions Per Month in 11 Epileptics During Five Months' Treatment with Nydrane, Compared with the Preceding Five Months

Case	Age	Average Fits per Month	
		Before Treatment	While Receiving Nydrane
1	33	36.6	19.2
2	46	4.8	5.8
3	32	11.0	9.0
4	46	8.8	5.8
5	53	1.8	3.0
6	40	6.6	5.0
7	28	6.0	2.4
8	44	2.6	3.6
9	37	2.8	0.8
10	31	10.6	7.4
11	33	4.8	3.0

The results are given in the Table. It will be seen that eight out of the eleven patients showed some improvement—that is, a reduction in fits—and this was quite considerable in one patient, who was the most severely affected in the series. Three patients had an increase in convulsions. There was no difference in the E.E.G. tracings. Four of the patients volunteered the information that they felt better during the time they were receiving the drug. Subjective assessments are justifiably suspect, but an increased alertness was also noted by nurses in charge of the patients.

Discussion

In considering the results it must be borne in mind that these patients were a highly selected group in that they were so severely disabled by epilepsy with psychosis that they required mental hospital treatment—that is, they were the most refractory type of epileptics. The number in the group was small, and for that reason it would not be profitable to apply statistical tests; nevertheless certain facts are evident, and the opinions expressed may be helpful to future users of the drug.

The most important fact which emerged from the trial was the lack of toxicity. Although the dosage was moderately high, especially when combined with other anticonvulsants, there was no evidence of depression of bone-marrow function and the white-cell count was always within normal limits. There was no evidence of liver or kidney damage. Nausea and diarrhoea were experienced by a few patients at first, but this was purely transitory and did not necessitate any adjustment in dosage.

The convulsion pattern showed, in general, a downward trend, which was considered satisfactory. One patient improved considerably and his convulsions were reduced from 36 to 19 a month. The others showed the usual fluctuation which one expects with anticonvulsants, and altogether eight were improved to some degree.

There have not been many trials carried out with nydrane, but the results given here appear to be very similar to those obtained by Hoenig *et al.* (1956) in a series of epileptics, including 19 who were in-patients of a mental hospital and apparently comparable to the patients treated here. Those workers also comment on the lack of toxicity and side-effects, although three cases developed status epilepticus during the withdrawal stage. They mention a subjective sense of well-being, which was also noted in a few patients in the present group. There appear to be two possible explanations of this—either that it is due to a direct stimulating effect of the drug on the cerebral cortex, or that it is a secondary effect following control of convulsions. The chemical formula of nydrane is certainly different from that of other anticonvulsants, but it seems unlikely that a drug which suppresses convulsions would also stimulate. It must be remembered, however, that the motor cortex is only a small part of the total brain substance, and a feeling of euphoria must be largely a summation effect. The E.E.G. did not indicate any great change in cerebral rhythms in those cases in which it was performed, but, in any case, it does not admit of sufficient refinement to be used as an index of mental activity.

Hoenig *et al.* comment on some loss of weight among their patients, with three cases of status epilepticus during the withdrawal stage, but such mishaps were entirely absent from the present series. It has been my experience that status epilepticus is provoked as often by a disturbance of homeostasis due to causes easily overlooked—for example, slight infection or constipation—as by cortical hyperexcitability due to drug imbalance.

The only minor disadvantage in the treatment was the number of tablets which the patient had to take in the day, especially when, as in this case, other drugs are given as well. The pharmaceutical chemist, however, may be able to find the answer to this.

In conclusion, then, I may state that we found nydrane a satisfactory drug to use. It was not the purpose of this trial to compare it with other anticonvulsants, but it does

appear to be synergistic or additive. We were particularly impressed by its safety and freedom from side-effects, and its action tends to counteract depression. Its judicious use should prove to be of benefit to large numbers of epileptics.

Summary

Eleven patients suffering from grand-mal epilepsy with psychosis were treated for five months with nydrane in addition to other anticonvulsants. The results were considered to be satisfactory by subjective and objective standards. Very few side-effects were observed, and in particular there was no evidence of any damage to liver or kidney or depression of haemopoietic function.

We thank the resident medical superintendent for permission to carry out the trial, and Rona Laboratories for their supply of the drug.

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PARTIAL GASTRECTOMY IN VON WILLEBRAND'S DISEASE

BY

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AND

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In the haemorrhagic diseases major operations are rightly held to be contraindicated except under the most desperate circumstances. To some extent von Willebrand's (1931) disease (pseudohaemophilia, constitutional thrombopathy) is an exception, and the following case is reported to show that the hazard of operation, though unpredictable, is not as great as is commonly supposed.

Case Report

The patient, a crane-driver aged 42, was one of a family of eight children. His father, one brother, and two sisters all suffered from a tendency to bleed. As a child he had been admitted to hospital on several occasions for severe nose bleeds, and at the age of 27 he had to have a blood transfusion for haemorrhage following a tooth extraction. On other occasions teeth had been extracted without incident. He had often noticed a tendency to easy bruising and had bled for as long as three to four hours after a cut while shaving. After a blood count he usually stopped bleeding at once, but had on one occasion continued to bleed for two hours.

This irregular bleeding tendency was investigated during 1954 and 1955. The bleeding-time (Duke) was generally prolonged. On eight occasions it was between 5 and 30 minutes and on five it was normal. The clotting-time and clot retraction were invariably normal. Hess's capillary fragility test was positive on 16 occasions, sometimes quite strongly, but on five others it was completely negative. The platelet count was always normal. Prothrombin estimations by the one- and two-stage methods and the thromboplastin generation test gave normal results. The family history and the evidence of a normal clotting mechanism associated with a prolonged bleeding-time and frequently positive capillary fragility tests confirmed the diagnosis of von Willebrand's disease, in which the cause of the haemorrhagic tendency is thought to lie in an abnormality of capillary function.

Since the age of 36 the patient had often been troubled by dyspepsia and gastro-intestinal haemorrhage. This was eventually shown radiologically and gastroscopically to be due to a lesser-curve gastric ulcer which healed once under medical treatment, only to recur later. In 1953 operation was thought to be indicated so far as the ulcer was concerned, but was not undertaken on account of the risk of haemorrhage. By 1955, however, the recurrent haemorrhages and increasing pain were causing severe disability, and it was evident that more drastic measures would be needed. It was decided to take advantage of the apparent variability of the haemorrhagic tendency and to operate when the bleeding-time was normal and the capillary fragility test negative.

Accordingly on August 5 laparotomy was performed by one of us: a chronic partly healed ulcer was found on the lesser curve of the stomach and a Billroth-I partial gastrectomy was carried out. No excessive bleeding occurred during the operation, but there was some continued oozing into the stomach for 48 hours afterwards, culminating in a brisk haematemesis, for which 5 pints (2,840 ml.) of blood was transfused. A five-day course of corticotrophin (100 mg. a day) was given, beginning 24 hours after the haematemesis. Recovery was uninterrupted, but there is no clear evidence that this drug affected the issue.

Three months after the operation the patient was very well, had no dyspeptic symptoms, and had put on half a stone (3.2 kg.) in weight.

Discussion

Von Willebrand's disease has recently been the subject of two able studies. Horler (1955) stresses the variability and unpredictability of the haemorrhagic tendency. He points out that the bleeding-time varies greatly from patient to patient, and in the same patient at different times. This agrees well with the experience of our patient, whose bleeding-time was normal on three occasions but prolonged, sometimes greatly, on others. Buchanan and Leavell (1956) have extended this observation by showing that the bleeding-times may vary when estimated simultaneously in different parts of the body. In a patient of theirs the bleeding-time was 17½ minutes in one ear and 180 minutes in the other.

This variability of the haemorrhagic tendency is reflected also in the patient's reaction to surgical operations. A patient may bleed heavily at one operation and no more than normal at another. In one of Horler's cases tonsillectomy led to severe haemorrhage, but a subsequent appendectomy was uneventful. This author's series included nine major operations in five patients. In five operations the bleeding was excessive and in four it was not. In one case the operation had to be abandoned on account of the bleeding, but there were no deaths. Buchanan and Leavell's experience was similar. Thirteen of their patients were submitted to surgery. Several bled heavily, but the haemorrhage was ultimately controlled in all cases. There were no deaths, and no operation had to be abandoned. In their review of the literature these authors show that among 199 reported cases of von Willebrand's disease 39 have undergone surgical operation (excluding the extraction of teeth), with only one death, which followed a splenectomy (Little and Ayres, 1928). Even allowing for the natural tendency for successes to be reported and failures forgotten, this is a remarkable fact, and contrasts sharply with haemophilia, in which the mortality of major operations is at least 50% (Biggs and Macfarlane, 1953).

The cause of von Willebrand's disease is unknown and there is no specific treatment. Therefore nothing can be done at operation to prevent haemorrhage apart from the most scrupulous attention to the usual surgical techniques of haemostasis. Buchanan and Leavell state that the bleeding-time is not always a reliable guide to the behaviour of the patient at operation. Yet it is the only guide of any sort which we possess, and it would seem reasonable to avoid an elective operation when the bleeding-time is greatly