HYPERSENSITIVITY TO BASAL ANAESTHETICS*

BY

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The investigation of problems arising in basal anaesthesia is very difficult, since so many factors go to make up the complete anaesthetic record of each case. To mention but a few of these factors, one may say that the patients are often in an abnormal state, either physically or psychologically, before the drugs are given; also, that in some cases other drugs are used in addition to the basal anaesthetic, and these complicate the picture. Furthermore, different operative procedures produce widely different effects upon patients, and these effects might be attributed in some cases to the method of anaesthesia and the drugs used. In view, therefore, of the difficulties to be encountered it would seem that accurate and full records of a large number of cases might furnish a valuable weapon with which to attack the problems involved. By observing factors that are common to many cases which react abnormally to basal anaesthetics, deductions as to their cause and prevention might be made. Perhaps it is no exaggeration to say that the drugs to which very few persons are hypersusceptible are the most difficult to investigate. An example of this is the use of paraldehyde: cases of hypersusceptibility to that drug are comparatively rare; but they do occur, and are very hard to explain, because comparison of common factors is almost impossible.

Avertin

Cases which are hypersusceptible to the action of this basal anaesthetic are more often seen, but are by no means common. As a result we know a little more about the causes of the hypersusceptibility to avertin. One of the most dangerous forms which this hypersusceptibility takes, but not the most common, is perhaps that of liability to liver-cell damage. In view of the similarity in chemical structure between avertin and chloroform, the comparison of their toxic effects is interesting. Both have a tendency to cause necrosis of the central cells of the liver lobules. The symptoms are very much the same with both drugs, and in the case of chloroform constitute what is known as delayed chloroform poisoning.

It has recently been shown that the liver extract of animals contains a substance which is able to protect liver cells from damage by small doses of chloroform. This substance has been isolated, and found to be sodium xanthine. When injected into animals sodium xanthine protects the liver cells from much greater doses of chloroform than those necessary to produce necrosis in normal animals. It is not unreasonable to suppose that the livers of people showing this form of hypersusceptibility to avertin might be deficient in this cell-protecting substance.

A recent case at the Royal Berkshire Hospital showed quite obvious symptoms of liver-cell damage following a dosage of avertin of 0.1 gramme per kilogramme of body weight. The patient recovered, and it was found later that she had revealed almost identical symptoms following chloroform anaesthesia twelve years previously. On the first occasion pure chloroform had been administered for thirty-five minutes; at her recent operation no chloroform was used.

The above illustrates the use that might be made of the previous anaesthetic history of a case to indicate a possible hypersusceptibility to avertin or any other basal anaesthetic.

The Barbiturates

In a series of 300 cases in which nembutal, sodium evipan, and sodium amytal were used forty-six showed hypersusceptibility in some form or other. The most common symptom was that of severe post-operative restlessness, for the control of which morphine was required in many cases. The next most common form was that of prolonged narcosis, which in one instance lasted for nineteen hours.

Other symptoms that suggested hypersusceptibility were:

- (a) Respiratory depression, which resulted in cyanosis in two cases.
- (b) A fall in systolic blood pressure to 90 mm. Hg.
- (c) The appearance of albuminuria, which persisted for four days in a patient previously albumin-free.
- (d) An increase in bronchial secretion, which resulted in cyanosis in a patient whose supplementary anaesthetic was nitrous oxide-oxygen only.

Certain conditions and diseases seemed to favour hypersusceptibility to a barbiturate, but they were by no means constant in the effects produced. They included:

1. Arteriosclerosis, especially when accompanied by high blood pressure.
2. Senility, even in the absence of obvious pathological changes.
3. Anoxaemia of the body tissues.
4. Toxaemia of bacterial origin. This was especially marked in the toxaemia due to the haemolytic streptococcus.
5. The presence of shock.
6. Pulmonary disease.

The use of the barbiturates in cases showing clinical evidence of hepatic disease was avoided.

Thirty-six cases of the series in which hypersusceptibility was suspected were given sodium amytal in a dose of half a grain per stone of body weight. Where necessary this amount was administered in a divided dose, and the effect of each dose was carefully observed. In twenty-four of these patients the suspicion proved to be justified, because twenty-two of them showed severe post-operative restlessness and two prolonged narcosis. These results suggested that although in some cases hypersusceptibility might be anticipated, this anticipation proved correct in only about 66 per cent. of cases.

It is probable that hypersusceptibility in an individual varies within wide limits. Some of the patients in this series had had repeated operations, and the same dose of the same drug was given on each occasion, the conditions being kept as nearly constant as possible. Fourteen cases were investigated thus, and not one showed hypersusceptible tendencies twice, though three patients had abnormal reactions to the drug on one of their visits to the operating theatre.

Another factor which seemed to influence the appearance of hypersusceptibility was the route by which the drug was administered. When given intravenously nembutal produced shorter periods of post-operative restlessness in certain susceptibles than when the oral route was used, but the symptoms appeared very much earlier after operation and were usually more severe. Prolonged narcosis and respiratory depression were more frequent

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when the intravenous route had been used. All cases in which the drug was given intravenously showed temporary albuminuria. In one case this persisted up to the fourth day.

The muscular contractions that were fairly common during and following the injection of evipan were not seen with nembutal used intravenously to the point of loss of consciousness. One out of the six healthy men who each received a fairly rapid intravenous injection of 10 c.cm. of cold sterile normal saline had an attack of shivering following the injection. This led to the inference that perhaps these muscular tremors are not a manifestation of hypersusceptibility to evipan in all cases.

In an attempt to detect hypersusceptibility to a barbiturate a test rather similar to the Schick test was devised. This was used in 210 cases. Into the skin of the forearm was injected 0.2 c.cm. of a 10 per cent. solution of sodium amytal, a control injection of sterile saline being made at the same time. The sites of injection were observed for the appearance of erythema. The results showed the unreliability of such a test in a very striking manner.

Conclusion

Hypersusceptibility is rare with the use of paraldehyde as a basal anaesthetic. Its explanation is very difficult in consequence, and cases are hard to anticipate.

More undue susceptibility is seen when avertin is used, and therefore rather more information as to the cause and avoidance of symptoms is available. Hypersusceptibility results in liver-cell damage in certain cases, and this may be due to the deficiency of a substance which normally protects the liver cells from necrosis during the detoxication of avertin.

With the barbiturates, hypersusceptibility is very inconstant, even in the same individual. Certain factors favour an undue reaction to a normal dose of the drugs, and though not absolutely constant these factors must be considered as a guide to dosage. No reliable test has so far been devised by means of which hypersusceptibility may be detected, and a skin test proved to be wholly unreliable.

Summary

It is suggested that deductions as to the cause and the prevention of hypersusceptibility to basal anaesthetics might be made by observing common factors in a large series of cases.

The liability to liver-cell damage from the use of these drugs is discussed.

Certain diseases and symptoms that suggest hypersusceptibility are recorded.

The route of administration is discussed as a factor in hypersusceptibility.

At the first public exhibition of its kind in the United States of America, held at the Harlem Art Center in New York City under the auspices of the Government's Federal Art Project and of the Bellevue Hospital's Psychiatric Division, 106 pictures were shown as the work of disordered minds. The artists included moronic children, chronic alcoholics, advanced epileptics, schizophrenics, manic-depressives, and victims of G.P.I. The majority of the exhibits told of mental conflicts and had but scant contact with reality, being shapeless (sometimes senseless), lurid, and gruesome. The idea underlying the art classes at Bellevue is to attempt a cure of the mentally sick by encouraging them to express their conflicts and at the same time to give psychiatrists a clearer picture of their patients' emotional life.

TREATMENT OF ACUTE OSTEOMYELITIS BY ULERON

BY

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My object in writing this note is not merely to record a short series of successful cases but to draw further attention to the use of uleron in the treatment of osteomyelitis. If it is of the value which I for the present am led to believe that it is, my belief can be confirmed by the observations of others, who I hope will put it to trial if they have not already done so.

The treatment of acute septic osteomyelitis demands the consideration of three problems: the relief of the abscess which is usually present; the treatment of the general infection, which in many cases manifests itself in the form of a virulent septicaemia; and the best method of dealing with the actual bone infection, which, although apparently responding satisfactorily to local treatment, may show a persistent tendency to recur, and this over a period limited only by the patient's span of life. For many years I have been interested in these problems, and after a close examination of the subject it seems to me that we cannot honestly maintain that our treatment has advanced much during the last twenty-five years, if we are to take as our criterion a highly improved mortality rate and an increased freedom from late recurrence of infection.

Practical experience over a long period improves one's judgment as to when to operate and as to the type of operation suited to each particular case; but it has been found that sera and blood transfusions are of very little value in the treatment of the severer types of septicaemia, and we still have to rely on Nature's powers of clearing up such infections. The liability of cases apparently completely cured to show severe and intractable recurrences years afterwards has, in my opinion, never received sufficient recognition. It is the knowledge of this liability to recur that has caused me always to be an advocate of complete subperiosteal resection in suitable cases.

The various forms of treatment advocated from time to time are familiar to us all, but the fact that they show such variety must surely mean that no one of them has been found to provide a complete solution to our difficulties. Hitherto no specific agent has been discovered that will really influence the staphylococcal septicaemia so often present, but my experience during the last year has led me to wonder whether we have not at last been offered something which, from the limited trial I have been able to give it, appears to be a curative agent worthy of more extended trial.

Five cases of acute osteomyelitis have been treated with uleron in addition to the ordinary local treatment. This drug, a sulphonamide preparation made by Bayer Products Ltd., has been used in tablet form (7½ grains). To young children we have given one tablet every four hours. The period over which it has been administered has varied up to several weeks.

The cases treated are few in number, but may be considered representative cases because they are all of the really severe type of osteomyelitis, and in each of four of them a different method of operative treatment was adopted; in the other no operation was done. Four were treated in the Royal Aberdeen Hospital for Sick Children, one in a nursing home.