scarlet fever, and diphtheria. Is it too much to hope that immunizing methods on the lines already introduced in the case of scarlet fever and diphtheria will eventually abolish these diseases, and at one stroke remove a large percentage of the worst type of discharging ear? The second factor is this: Chronic discharge of the middle ear is a disease of the poorer classes. It is a disease which is fostered by poor feeding and bad housing. Many an ear which has failed to respond to all methods of treatment has dried up entirely when the unfortunate child is removed from his own surroundings and sent to a convalescent home in the country or seaside for three to six months. Unfortunately economic conditions prevent the parent from keeping him in decent surroundings, and when the child returns home it is only a question of a few weeks before the discharge recurs.

THE SIGNIFICANCE OF URINARY "PROTEOSE" IN IDIOPATHIC EPILEPSY

BY

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Of recent years idiopathic epilepsy has come less and less to be looked upon as a disease of the brain and has become to be considered a symptom-complex with cerebral and nervous manifestations. With this changed outlook it is natural that various theories of extracranial causation should have been more or less completely investigated.

AETIOLOGY

The most widely accepted hypothesis of the causation of epileptic fits is that which postulates the presence of some convulsant toxin in the circulating blood. Much experimental work has been done to demonstrate the plausibility of this, and fits closely resembling, if not identical with, those found in clinical epilepsy have been produced by the administration of various toxic substances. Magnan,¹ one of the earliest workers in this line of approach, produced fits, both in human beings and in dogs, by oral administration and intravenous injections of absinthe, while Rhoeber² and others produced similar results with picrotoxin. Purkinje succeeded in obtaining epileptiform fits in himself by taking appropriate doses of camphor, and Muskens³ and others have carried out extensive experiments on the fits produced by camphor monobromide.

The conclusion reached by all the observers was that the fit was a direct response to the presence of the particular poison in the circulating blood. It was a normal physiological response, the result being to "discharge" the animal for the time being—probably by breaking down the toxic material to some innocuous substance. Thus Wiedemann⁴ found that when recovery took place from the epileptiform fits produced by camphor, all the camphor was excreted in the harmless form of uramido-camphoglycuronic acid and camphoglycuronic acid, and he considered that the fits themselves had caused this breakdown.

All this work, though of considerable value from the point of view of pure science, in the demonstration of the exact nature of myoclonic reflexes threw no light on the actual causation of true epilepsy.

Periodically observers (particularly Pagniez, Mouzon, and Turpin⁵) have reported that they have withdrawn the blood from epileptics during fits and have injected this into normal people, producing in them convulsions. This seems to support the hypothesis of a circulating con-

vulsant, but Goodall⁶ and others, working at the Cardiff City Mental Hospital, report that they have been unable to demonstrate the toxicity of either the blood or cerebrospinal fluid in epilepsy or in psychotic conditions. On the other hand, Loewe⁷ has stated that he has been able to extract from the urine of epileptics an insoluble adialysate which, when injected intravenously, was capable of producing convulsions identical with those of epilepsy, though an adialysate similarly prepared from the urine of normal people proved non-toxic.

To explain the periodicity of epileptic fits and the production of an endogenous convulsant poison various views have been brought forward, and many observers consider that the disease should be grouped with migraine and asthma as an allergic manifestation. In 1924 Collier⁸ suggested that epilepsy was probably a metabolic dyscrasia, and cited reports of good results obtained by removing the blood from epileptics and attempting to desensitize the patients to their own serum—presumably on the assumption that it contained some fit-producing material (see above). On the other hand Worster-Drought⁹ reported that, working on the idea of the supposed relationship between epilepsy and asthma, he had carried out a series of cutaneous reactions for protein sensitization with common food extracts on forty cases of idiopathic epilepsy, and had failed to obtain a single positive reaction.

ACCOUNT OF INVESTIGATION

In view of these conflicting results it was decided to carry out certain tests on the epileptics in this hospital.

Favourable results having been reported in the district on the treatment of cases of asthma and migraine by injection of "urinary proteose" as recommended by Oriel and Barber,^{10, 11} it was decided as a preliminary to examine the urine of epileptics for the presence of these substances. Sixty-eight unselected cases were taken and all treatment temporarily stopped. The urine was tested, and in forty-eight cases (71 per cent.) "proteose" was found to be present; in 47 per cent. of these it was found to be present in considerable amounts. It was decided that no useful purpose would be served at this stage in attempting to estimate the amount quantitatively. Urine specimens were next taken and actual specimens of the "proteose" extracted by the method recommended by Oriel.¹² The so-called "proteose" we found to be a greyish-white powder, insoluble in water or ethyl alcohol, but readily soluble in ether. Fresh specimens, it was found, dissolved rapidly in decinormal sodium hydroxide, though specimens that had been kept for two or three days dissolved less easily, probably indicating that they had undergone some chemical or physical change. Solutions were made in decinormal sodium hydroxide and subjected to various chemical tests. Consistently negative results were obtained with Millon's test, the biuret and xanthoproteic reactions, to which positive results were reported in all cases by Barber and Oriel in the urinary "proteose" of asthmatics.¹¹

Ten epileptics were next taken and, all treatment having been stopped, urine specimens were collected and extracted, the resulting "proteose" being made up into sterile solutions at dilutions of 1 in 10, 1 in 100, and 1 in 1,000. Into the anterior aspect of the forearm of each case 0.1 c.cm. of a 1 in 1,000 solution of the patient's own "proteose" was injected intradermally; while into the other arm a corresponding volume of similarly diluted caustic soda was injected as a control. The arms were examined every ten minutes for an hour, and then at half-hourly intervals for four hours. In all cases a slight area of erythema rapidly developed round the site of inoculation, but in no case was any characteristic wheal produced indicating hypersensitivity towards the injected material, and in no case was the erythema more marked in the

"proteose"-injected arm than in the control arm. The only interesting fact that emerged was that one of the injected patients developed a severe urticarial rash the next day, which, it was considered at the time, might be due to a sensitivity towards the injected "proteose."

A week later the same ten cases were taken and again injected, this time with a different "proteose." Five were injected intradermally with 0.1 c.cm. of a 1 in 1,000 solution of a "proteose" obtained from another epileptic, two were injected with a similar volume of a "proteose" obtained from the urine of an asthmatic, and three with a "proteose" from a case of migraine, the last solutions being kindly supplied by Dr. E. N. Davey, the pathologist to the Gloucestershire Royal Infirmary. At the same time three normal healthy persons were injected with a similar amount of epileptic "proteose." Again no reaction was produced in any of those injected.

At the end of another week a further series of injections were given, using a 1 in 100 solution, but with these again no reaction indicating sensitivity was produced.

Attempts at Desensitization

The above results were considered to have proved that cases of epilepsy possess no skin sensitiveness to "proteoses" from their own urine or from the urine of asthmatic or other related diseases, but it was considered that it might be feasible to suppose that the "proteose" in the urine might be a specific cerebral irritant, and might even be identical with the adialysate described by Loewe⁶ or the toxin present in the blood mentioned by Pagniez and others.⁷ Working on this hypothesis it was decided to attempt to desensitize certain patients to "proteose."

Ten cases were again taken. Seven of these were treated with their own "proteose," two with "proteose" from other epileptics, and one with "proteose" from an asthmatic. In all the cases subcutaneous injections were given at weekly intervals, starting with 0.1 c.cm. of a 1 in 100 solution, the dose being doubled every week till, finally, 3.2 c.cm. were given. The following results were obtained. The two cases injected with other epileptics' "proteose" were unchanged and the patient injected with asthmatic "proteose" was unchanged. Of the seven cases injected with their own "proteose" four showed absolutely no change in the number or force of the fits, or in their general mentality. At the end of the course of injections one patient who regularly had fits nearly every week went for three weeks with no fits, and for the time being showed an improvement in mental outlook. She has since relapsed, and has become worse than before. One patient who was previously having strong major fits, almost daily, has since had mostly minor fits, though the frequency has been unchanged and the typical epileptic mentality persists. The last patient, who always has a bout of four or five fits once a month followed by a week of marked mental confusion, went for two months with no fits, and although the fits have now returned, she is mentally almost normal and her fits are not followed by the semi-stuporose state.

DISCUSSION

These results, though taken from far too small a number of cases to be conclusive, point to the fact that the "proteose" of the urine of epileptics is not of great fit-producing significance, and that it is unlikely to be the same substance as Loewe's adialysate.

Certain facts which we elicited, however, tend to point the other way, and might be looked upon as showing that the urinary "proteose" is of importance either as a convulsant toxin or is in some way related to the production of fits. Thus it was found in those patients whose fits are controlled by luminal (phenyl barbitone) treatment, the "proteose" tends to vanish from the

urine, but when the luminal is stopped and the fits return the "proteose" appears again in the urine. But in those cases where no benefit was derived from luminal administration it was found that the drug had no influence on the amount of "proteose" excreted. Another point of interest which came to light was that when an epileptic has a bout of fits, the urine is loaded with "proteose" at the commencement, but specimens withdrawn at intervals contain decreasing amounts, so that finally, at the end of the bout, when the fits stop, no "proteose" is discovered. This seems to fit in with the theory of Muskens and others that the fits "discharge" the subject by causing the body to destroy the circulating convulsant toxin, which, from the last observations, might well be the "proteose" or its precursor.

It is obvious from these contradictory results that no definite conclusion can be drawn, and it is yet to be proved or disproved that urinary "proteoses" are of significance in this type of case. It would probably be better, particularly as considerable doubt has of late been thrown on the specificity of "proteose" in other definitely allergic conditions,^{13 14} to await further reports from the Asthma Research Council before continuing work on these lines.

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TREATMENT OF MALIGNANT DISEASE BY PITUITRIN AND THEELIN

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Susman (*British Medical Journal*, October 31st, 1931) claimed a certain amount of success in the treatment of malignant disease by the administration of pituitrin and the ovarian hormone oestrin (theelin), combined with a diet low in carbohydrate. It was of interest to discover whether these results could be verified by independent workers. A few cases have been so treated in the Royal Infirmary, Glasgow.

Cases were chosen in which no doubt existed as to the diagnosis. The tumours were submitted to microscopical examination, and this was repeated at intervals in several of the cases. During the treatment the patients were put on a diet low in carbohydrate and the twenty-four-hourly excretion of urine was charted.

CASE REPORTS

Case 1.—Squamous-celled carcinoma of the anal margin. Male, aged 56. There had been haemorrhage and swelling around the anus for some ten months. On admission, two large malignant polypi were found protruding from the anus, with induration and ulceration around the anal canal.