suspicious of any such surgical procedures. Histopathological examination confirmed the view that the nerves were abnormal, for extensive myelinic degeneration was found to be present. The patient was discharged to her own home convinced that her pains had gone and that the head noises were less severe, presumably due to lowered nervous tension generally. Unfortunately, before the progress of the case could be further observed, she developed influenza and died from bronchopneumonia.

Conclusion

This patient, then, suffering from what appeared to be a characteristic "functional" or "dynamic" variety of psychosis, typical both in development and in end-result, finally proved to have as the central symptom and major precipitating factor a disorder of a purely organic and remediable nature. Apart from the obvious queries as to the general level of integrity of the nerve structures

in such a patient, loaded by a developmental failure of buccal structures, one finds this case history significant along general lines. It adds one item of information to the complex situation of "functional" and "organic" in nervous disease and to the problem generally of the very common cephalalgias met with in this field.

The case is one of depression developing as a reaction to an unhappy life situation. Paranoid features appear, due to the interpretation by the patient of a painful symptom. The weight of presumptive evidence suggests that the pain is "functional." Investigation puts this in some doubt. The pain is finally proved to be organic in origin. The question is posed as to what the progress of the case would have been if the painful symptom had been treated at its outset seven years before, and attention is drawn to the need for the recognition of the association of functional and organic features in psychotic and neurotic states.

AGRANULOCYTIC ANGINA

A CASE OF THE RELAPSING TYPE

BY

A. DALY BRISCOE, M.A., M.B., B.CHIR.

Morris, Miller, and Thacker Neville,¹ in reporting a case of agranulocytic angina recently, remark that "as the number of recorded cases in this country is still small, it is well that every accredited case should be reported with as full notes as possible on symptoms and treatment."

Amidopyrine and its allies have been thought to be causative agents in some cases, but in this case, as in my previous one,² it cannot be so. After the commencement of one of the attacks the patient was given four sedormid tablets, but as soon as the diagnosis was made these were stopped, and no drug of this character was taken before the final relapse. Apart from the problem of aetiology that of treatment has also been difficult, and the value of pentnucleotide, which was thought at first to be very great, is now being questioned.

My first case, that of a man of 71, recovered without having any pentnucleotide, and is still quite well now. In this present case it was thought that pentnucleotide had been responsible for the recovery in the December attack, but in view of subsequent events doubt must be cast on its value.

Case History

A woman aged 59 years had always enjoyed good health and had had three children, all alive and well. In April, 1934, she had what was apparently an attack of tonsillitis, which quickly subsided, and she was well again within a week. On November 15th, 1934, she again developed tonsillitis, with a temperature of 102° F., but was more ill than in April: the throat had the appearance of a follicular tonsillitis, and a throat swab was reported on as follows:

"No diphtheria bacilli present: cultures give a growth of *Streptococcus longus* which is non-haemolytic, and a yeast: the former produced 95 per cent. of the colonies and the latter 5 per cent."

The patient, when once over the initial stages, made a good recovery, and was about again after twelve days; then on December 17th, 1934, having been quite well up to the previous evening, she fell suddenly acutely ill with a sore throat and high temperature. This time the degree of toxæmia seemed much greater than before. The report on the throat swab was:

"Direct examination of this swab shows debris only; cultures, however, resulted in a mixed growth of the following organisms in about the stated proportions: haemolytic *Streptococcus longus*, 35 per cent.; non-haemolytic *Streptococcus longus*, 30 per cent.; *Streptococcus brevis*, 20 per

cent.; *Staphylococcus albus*, 15 per cent.; no Klebs-Loeffler bacilli were cultured."

On December 21st her condition was definitely worse, and streptococcus (scarlatinal) antitoxin 10 c.cm. was given and a blood film taken; the report on this was: polymorphs, nil; lymphocytes, 92.4 per cent.; mononuclears, 7.6 per cent.; eosinophils, nil.

The diagnosis was now made and pentnucleotide 10 c.cm. was given twice daily. Gradually the exudate spread from the left tonsil all over the soft palate, and the right side was also involved. On December 21st and 22nd there were occasional erythematous patches of a blotchy character to be seen over the arms, and three days later these were seen on the abdomen. The pulse became intermittent at times and swallowing was difficult. A throat smear of December 22nd was reported on:

"Direct examination of this smear shows epithelial cells and various organisms, including many streptococci: no polymorphs were present."

There were signs of the huge slough that had formed separating on December 23rd, and on the following day the soft palate showed patches where the slough had come away.

The sloughs continued to separate, and on December 27th it looked as though a portion of the left tonsil had sloughed off, and the uvula appeared smaller and shrunken. Steady progress followed, but there was a slight reappearance of the exudate on January 1st, but by January 10th there was no sign of slough or exudate. During this illness the patient remained mentally alert. When drowsy she was perpetually groaning, but on being roused was at once normal and did not seem to realize that she had been making a noise. This behaviour was repeated in the subsequent attack.

The fever lasted nine days, and although clinically convalescence appeared to be uninterrupted, yet the blood counts did not improve as consistently as was desired. Three further injections of pentnucleotide were given and four of sodium nucleinate 2 c.cm., but neither had any pronounced effect on the blood counts. After February 19th no special treatment was given, and on March 15th the total white count reached 7,080, with 59.2 per cent. polymorphs: the various blood counts are appended below.

On July 22nd she went a journey of thirty miles to see her son; she began to feel unwell while having tea, and on arrival home that evening complained of a sore throat. Her temperature was already 102° F. and there was a slight exudate on the left tonsil; 20 c.cm. of pentnucleotide was given at once, and this was followed by vomiting. On the following day there was an exudate on both tonsils; vomiting occurred again

after the injection of pentnucleotide 10 c.cm. This amount was given twice daily, and when the patient was distressed coramine was injected. On July 24th there was again a blotchy eruption on the abdomen and lower part of the chest, and some exudate was seen on the posterior pharyngeal wall. The tongue and mouth were very dry and there was some diarrhoea. On the next day dysphagia was marked and the pulse became intermittent. On July 26th a small anal ulcer was seen. The throat sloughs were now very large, covering most of the fauces as before. On July 28th Cheyne-Stokes breathing was noticed when the patient was asleep. Much offensive sputum was coughed up, suggesting that sloughs were separating further down the pharynx and oesophagus. The report on the sputum was:

"Direct examination shows epithelial cells, no pus, many Gram-positive and Gram-negative cocci. Cultures resulted in growths of the following organisms, the approximate percentage of each being shown from a rough colony count: haemolytic *Streptococcus longus*, 10 per cent.; pneumococcus, 40 per cent.; *Micrococcus catarrhalis*, 50 per cent."

A second anal ulcer was observed on July 28th. By July 29th the patient was becoming increasingly weaker, the sclerotics appeared yellow, the sputum was foul-smelling and yellow in colour, and by 2 a.m. on July 30th she was semi-comatose; by 7 a.m. she was completely unconscious, and died at 1.30 p.m. The temperature rose to 106.6° F. before death.

Examination of a blood film on July 29th showed that:

"Many of the lymphocytes are larger than normal, with more cytoplasm, which stains more deeply than usual."

Immediately after death the patient became a vivid yellow colour, with purple patches beginning in the face and continuing down the limbs and all over the body.

Comment

In this patient for some reason the manufacture of polymorphs became irregular early in 1934, and the attacks in April and November must, in view of subsequent events, be regarded as due to a condition of mild agranulocytosis. The red cells appeared to be unaffected, and a count on December 24th revealed 4,650,000 red cells per cubic millimetre, with haemoglobin 74 per cent. Polymorphonuclear leucocytes were known to be absent for four days in the penultimate attack. The pentnucleotide treatment appeared to be responsible for the recovery in December, 1934, but in the illness of July, 1935, the patient never showed any response to it, the total white count continuing to fall till it reached the very low figure of 210 per cubic millimetre. Death in coma with hyperpyrexia also occurred in the case reported by Fairley and Scott.³

It would seem that this malady is more prevalent than is at present thought to be the case; it might therefore be wise in all cases of severe tonsillitis to examine the blood in order to exclude the possibility of agranulocytic angina.

Table of Blood Counts

		Percentage of Polymorphs in Differential Count	Total White Cell Counts
December	22nd, 1934	0.0	705
"	24th, "	0.9	580
"	26th, "	19.0	1,720
"	30th, "	41.0	3,070
January	5th, 1935	44.1	3,715
"	18th, "	19.4	2,030
"	23rd, "	24.8	3,750
"	28th, "	43.0	3,500
"	30th, "	44.0	2,670
February	5th, "	36.0	4,120
"	12th, "	42.0	3,850
"	19th, "	50.5	3,500
March	15th, "	59.2	7,080
June	20th, "	44.5	3,060
July	22nd, "	0.7	2,200
"	24th, "	0.0	930
"	26th, "	0.0	560
"	27th, "	0.0	270
"	29th, "	0.0	210

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SOME EXPERIMENTS WITH PROTAMINE INSULINATE

BY

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AND

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One of the most obvious difficulties in the use of insulin in diabetes is its short-lived and often too violent action after injection. Thus in many severe diabetics a high fasting blood sugar (300 to 400 mg. per 100 c.cm.) may be rapidly reduced to normal, perhaps to hypoglycaemic levels, in three to five hours, but is maintained at this level for only an hour or two and, when the insulin action is over, rises to hyperglycaemic levels as quickly as it fell, with a return at the same time of glycosuria and ketonuria. Such patients run the risk of a dangerous alternation between clinical hypoglycaemia and hyperglycaemia with ketosis. Attempts have been made to slow and prolong the action of insulin, but the first important success has only recently been obtained by Dr. Hagedorn and his colleagues in Denmark. After two to three years of work they have discovered a compound of insulin and a protamine (protamine insulin*) which by virtue of its low solubility in the tissue fluids is very slowly absorbed. One of us had the privilege of seeing the clinical results obtained by the Danish workers, and their experiences,^{1,2} with confirmatory results from America,³ have just been published.

The advantages claimed are: (1) Its prolonged action, which can therefore keep the blood sugar normal for longer than ordinary insulin. It is stated to act "about twice as long," and a normal fasting blood sugar can therefore be obtained before breakfast. (2) A reduced liability to hypoglycaemia because of its slower and less violent action. The disadvantages pointed out in their publication are: (1) The instability of the protamine compound if kept for more than three to four weeks. (2) Its inability to control the hyperglycaemia which follows carbohydrate meals.

Hagedorn's present clinical practice is therefore to give insulin in the morning to deal with the day's carbohydrate food, and protamine insulin (P.I.) at night to keep the blood sugar in control until the next morning's dose. In our opinion some patients might find the use of two sorts of insulin very confusing.

By the courtesy of Dr. Hagedorn we have received a supply of protamine insulin for experimental purposes, and have obtained complete confirmation of his results. We have extended our experiments to investigate in more detail its clinical action and possible uses and limitations. In all our investigations the blood-sugar estimations were controlled by simultaneous urine samples tested for sugar and ketones by qualitative methods. The latter, which are seldom published, were in every instance confirmatory.

* "P.I." will be used for the new insulin compound and "I." for the present form.