Relief of Hypertensive Symptoms by Ecolid, with Side-effects

Preliminary studies suggest that patients starting treatment with ecolid lose symptoms attributed to hypertension, particularly headache and dyspnoea, as rapidly as would have been expected had they been treated with pentolinium. Two such patients, however, after only one week's treatment developed nausea, and, in one, vomiting followed each injection. These symptoms were completely relieved by the substitution of parenteral pentolinium for parenteral ecolid. Otherwise the side-effects so far observed with this compound are similar to those resulting from administration of other ganglion-blocking agents. Some patients who were fully familiar with the side-effects resulting from pentolinium were of the opinion that constipation and blurring of vision were less troublesome with ecolid. In one patient, however, the visual blurring was greater with ecolid. It might be particularly useful in the treatment of those patients who have troublesome side-effects with pentolinium.

We have 15 patients who have been maintained on ecolid for periods ranging from one to eight months. Four of these have been maintained on parenteral therapy: the remaining 11 were stabilized on oral ecolid, six of them having started treatment with the parenteral preparation of the compound (Table VIII). The response to therapy shown by this group of 15 patients has been no different from that encountered with pentolinium—two suffering from hypertensive heart failure and two others suffering from malignant hypertension showed the customary rapid improvement seen in the treatment of these conditions with other ganglion-blocking agents.

A comparison of ecolid has been made with pentolinium in four of these patients. It should be pointed out that as all of these four were selected because they had shown unfavourable reactions to pentolinium, and as the numbers are very small, our experience does not allow us to compare the relative comfort of patients controlled by pentolinium and those by ecolid. What is, however, apparent to us is that some patients are more comfortable on pentolinium and others on ecolid. We had suspected beforehand that "large dose" patients might be better on the more active drug; and in some instances, at least, this proved to be so—for example, two patients who developed paralytic ileus on pentolinium have both been maintained without trouble, and very little discomfort, on ecolid.

On the other hand, three patients who started treatment with ecolid developed unfavourable reactions to this drug: all preferred pentolinium on being changed to this therapy.

Our only firm conclusion is that ecolid merits further clinical trial.

Summary

Ecolid, a new hypotensive agent, has been tested, and its action compared with that of pentolinium, in 28 patients suffering from hypertension.

Parenteral ecolid is slightly more than twice as potent as parenteral pentolinium, and is similar to pentolinium in its course of action.

Patients show drug toleration, so that daily increases in dose are necessary during the early stages of treatment. With the development of toleration there develops a cross-toleration to pentolinium. The hypotensive effect of the drug is increased by standing, and also by meals.

Parenteral ecolid, on an average, is 15 times as potent as oral ecolid.

Preliminary observations encourage a more extended trial of its suitability for the treatment of hypertensive disorders.

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TREATMENT OF MIXED PAROTID TUMOURS

BY

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Mixed tumours of the salivary glands are not infrequently encountered in clinical practice, 90% occurring within the parotid gland. Although tumours other than "mixed parotid" do occur within this gland, these growths form approximately 90% of the total. Two controversies arise in relation to these tumours: firstly, their pathogenesis, and, secondly, the correct method of treatment. A considerable literature on the pathogenesis of these tumours has appeared since the initial description by Kaltschmied (1752). Billroth (1859) believed the tumour to be mesodermal in origin; Virchow (1863) regarded it as epithelial, with metaplasia occurring to produce the "cartilaginous" areas; whilst Kaufmann (1881) attempted to prove a relationship to endothelial structures on the basis of peritheliomatous and sarcoma-like features.

By 1900 opinion had reverted once more to the epithelial nature of these tumours, and Willis (1948), firmly supporting this theory, has called the tumour a pleomorphic adenoma or adenocarcinoma, thus excluding the variety of names which had arisen: this complex nomenclature had sought to describe the dominant histological features which tend to vary from tumour to tumour. Willis regards all these tumours as malignant, although in many cases the grade of malignancy is low. McFarland (1936), in a clinico-pathological study, came to the conclusion that no relationship could be established between the histological picture and the clinical course of mixed parotid tumours.

Opinions regarding treatment of these tumours still differ. The older surgical method consisted of an intracapsular enucleation; but, later, extracapsular enucleation, with or without the addition of irradiation

in some form, was advocated. The recurrence rate, however, has remained high. McFarland (1936) reported a recurrence rate of 23.3%. More recently, radical excision of that part of the parotid gland containing the tumour has been advocated, a method of treatment which must be combined with a technique that preserves the facial nerve.

The present paper reports the results of the older, more conservative forms of treatment as determined by a long-term follow-up of a series of patients, outlines a plan of treatment for mixed tumours of the parotid, and urges a more radical primary operation combined with radiotherapy: a technique for this operation is described.

Follow-up Study of the Results of Treatment

A recent survey was made of the results obtained in 80 consecutive cases of mixed parotid tumours referred to the radiotherapy department at Leeds during the years 1935-49 inclusive, the follow-up period being from six to twenty years. Included in this series were three recurrent cases presenting for treatment within this period, the primary treatment having taken place before 1935. As radiotherapy in some form has been used concurrently with, or considered as an adjunct to, surgery in the treatment of mixed parotid tumours during the period under review, it is probable that these 80 patients represent nearly all the cases of mixed parotid tumours seen in this centre during that time.

Age at Onset of Tumour.—Analysis of the recorded age at the onset of the tumour shows that these growths occur at almost any period of life, but in this series no tumour was manifest to the patient before the age of 15 years. The remaining decades show an almost equal incidence (Table I).

Duration of Tumour Before Treatment.—Table II shows that in spite of the slow growth of these tumours 46% of the patients presented themselves for treatment within three years of first noticing a swelling in the region of the parotid. However, 15% of the patients presented themselves ten to twenty years after noticing a swelling. It is reasonable to suppose that in these patients the tumour grew exceedingly slowly, for no growth was described as massive in size when first seen.

Recurrence Following Treatment.—Table III shows that most of these tumours were treated by surgery plus deep x-ray therapy. Although precise operative details are lacking it is probable that nearly all the tumours were removed by intracapsular enucleation, although some would undoubtedly be excised with the capsule. The overall recurrence rate is seen to be 30%. Although the series when

TABLE I.—Age at Which Tumour was First Noticed by Patient (71 Patients; Unknown in 9)

No.	2	12	7	9	5	10	7	3	8	1	3	4
Age (years) . .	15-	20-	25-	30-	35-	40-	45-	50-	55-	60-	65-	70+

TABLE II.—Duration of Tumour Before Patients Presented for Treatment (61 Patients)

Duration in years	1-	2-	3-	4-	5-	10-	20-	30+
No. of patients . .	15	15	7	6	5	3	8	2

TABLE III.—Frequency of Recurrence after Different Forms of Treatment

Type of Treatment	No. of Cases Treated	No. of Cases Developing Recurrence
Enucleation alone	19	16
Enucleation plus deep x-ray or radium beam therapy . .	44	4
Enucleation plus interstitial irradiation	11	0
Deep x-ray therapy alone . .	5	4
Enucleation plus deep x-ray therapy plus interstitial irradiation	1	0
Total	80	24 (30%)

broken down presents small groups of cases, it is immediately evident that the simpler forms of surgery without the addition of radiotherapy are followed by a high recurrence rate; the largest series, comprising 44 cases, also shows a recurrence rate of 9%. Enucleation plus interstitial irradiation, although a small group, shows no recurrences during the period under review.

Time Interval Between Treatment and Recurrence.—Table IV shows the interval of time between treatment and recurrence. The majority of recurrences occur early following treatment, many within one year and nearly all within

TABLE IV.—Interval of Time Between Initial Treatment and Development of Recurrent Tumour (24 Recurrences)

No. of patients	12	5	3	2	2
Period in years within which recurrence occurred	1	5	10	30	≥40

TABLE V.—Results of Treatment of Recurrent Tumours

Mode of Treatment	No. of Cases	Recurrences	Deaths
Excision alone	7	4	
Deep x-ray therapy	6	1	1
Excision plus deep x-ray therapy	5	2	2
Excision plus interstitial irradiation	3		1
No further treatment	3		3

five years. In this series three patients are included who were treated for recurrences during the years surveyed. These patients had been initially treated over 20 years previously. Thus an assessment of any mode of treatment based on a five-year follow-up will tend to give an incomplete picture of the recurrence rate.

Treatment of Recurrent Tumours.—Table V again demonstrates the inadequacy of the simpler surgical methods; following simple excision in seven cases, recurrence occurred in four. Out of a total of 24 recurrences 7 deaths occurred; in only 2 of these patients was a post-mortem examination performed: secondary deposits were found in the cervical spine in one, and in the other metastases were present in the brain. In five patients death occurred at home, the follow-up notes describing extensive local recurrence with deterioration of the patient's general condition.

Discussion of Causes of Failure

Patey (1930) suggested that there were three probable causes of recurrence: firstly, cells might be left behind at the primary operation; secondly, tumours might be multiple at the time of the primary operation; and, thirdly, a further tumour may develop at a later date. A fourth type of recurrence might be added—the early recurrence resulting in death following excision in tumours which have been present for many years. This probably represents a group in which interference with the tumours has led to malignant

FIG. 1.—Recurrent parotid tumour excised by radical operation. Main tissue mass lying to the left, with an islet of tumour cells present in the capsule.

degeneration. The time interval between excision and recurrence (under five years in the majority) suggests that the most common cause of recurrence is inadequate excision of tumours at the initial operation. That this may very easily be done is shown in Fig. 1, which is a section of the border region of a recurrent parotid tumour removed by radical excision. Surrounding the tumour is the capsule, and within the capsule is a small group of tumour cells. In only one case of the 80 reviewed were multiple tumours found at a second operation. In four cases in this series treatment was directed to a recurrence which had followed original excision over 20 years before. It is reasonable to suggest that these tumours represent the development of completely new neoplasms in the gland. In two cases death resulted almost immediately following excision of a tumour which had been known to be present for many years, suggesting that two factors were in operation: firstly, tumour tissue had been left *in situ*, and, secondly, some change had taken place in these cells, leading to rapid and "malignant" recurrence.

Table VI classifies the suggested cause of recurrence and shows the predominant cause—that is, incomplete excision. In three cases in group 1 it is reasonable to assume that the primary tumour was malignant, since in these cases, following the initial treatment, death occurred within a short period.

TABLE VI.—*Suggested Cause of Recurrence*

	Cases
Group 1: Tumour cells left behind at operation	17
.. 2: Multiple tissues within the gland	1
.. 3: Recurrence due to new tumour	4
.. 4: Early malignant recurrence	2

The remainder, however, represent recurrences which might have been avoided if more radical surgery had been employed at the time of primary treatment. Following radical surgery, however, the analysis of results (Table V) suggests that irradiation in some form should be used. If radical surgery is to be carried out, a method must be used which will avoid injury to the facial nerve. If the tumour arises in the anterior part of the gland, then surgery cannot at any time be radical without injury to the nerve; but fortunately the majority of these tumours arise in the posterior part of the gland behind the ramus of the mandible, and it is with growths in this situation that radical surgery with preservation of the facial nerve is possible.

Technique of Radical Excision with Preservation of the Facial Nerve

The surgery of parotid neoplasms has been dominated by fear of injury to the facial nerve. McFarland (1936) suggested that the tumour be allowed to remain *in situ* until "ripened"; this, he thought, made for easier excision. It is, however, against all surgical principles to allow a malignant tumour to remain *in situ* following diagnosis. Isolation of the facial nerve, therefore, is the crux of the problem. If this can be done, then dissection superficial to its ramifications can be performed.

Sistrunk (1921) and Adson and Ott (1923) described distal identification of the inframandibular division of the facial nerve. Once this preliminary step is taken the smaller branches are followed proximally to the main stems. There are, however, disadvantages to this method of approach. Firstly, the nerve in this situation is thinning out and bears a variable relationship to the angle of the mandible. Secondly, once it has been identified at this point its further display involves a very tedious dissection in retrograde fashion into the tumour-bearing area.

Shucksmith *et al.* (1951) demonstrated by anatomical dissection that the facial nerve passes 0.6 cm. below the tympanic plate and may be isolated by reference to this landmark at operation. A similar technique has also been followed by Martin (1952) and by Ariel *et al.* (1954). This method of treating the nerve below the level of the stylomastoid foramen may be extremely difficult because anatomical landmarks at this level are few in number.

The following method of approach is therefore suggested as an alternative; it has been evolved as a result of 20 post-mortem dissections of the facial nerve and related structures.

A longitudinal incision is made from the level of MacEwen's triangle a fingerbreadth behind the pinna, running downwards and forwards along the anterior border of the sternomastoid process. The external carotid artery is identified and ligated within the confines of the carotid triangle. Attention is then directed to the mastoid process. The attachments of the sternomastoid and the periosteum are stripped off the bone and the tip is removed by hammer and chisel. Deep to the process the fibres of the posterior belly of the digastric muscle will be seen running downwards and forwards from the digastric groove. To allow greater access to the region, and to identify the groove correctly, these fibres are reflected downwards, starting the dissection posteriorly. This manoeuvre allows a probe to be placed in the groove along its long axis. Fig. 2 is a photograph of the undersurface of the mastoid bone, and demonstrates that a

FIG. 2.—Inferior surface of right temporal bone, illustrating the axis of the digastric groove and the point of emergence at the facial nerve from the stylomastoid foramen.

probe placed along the digastric groove points to the plane of emergence of the facial nerve from the stylomastoid foramen. After its identification, the nerve, a structure approximately 3 mm. in diameter at its exit from the canal, may be traced downwards and forwards without danger to the main branches, which leave the nerve on its anterior aspect, the first major division occurring within 3 cm. of the foramen.

As the major divisions are isolated, the parotid gland can be dissected from their superficial surface, which will result in an almost complete parotidectomy.

Scheme for Management of Parotid Neoplasms

The following plan is suggested for the treatment of tumours of the parotid gland. After clinical diagnosis extra-capsular excision biopsy of the tumour should be performed; if the histological report shows that the tumour is of the adenolymphoma group then no further treatment will be required, these neoplasms showing no tendency to recur (Plaut, 1942). If the report is one of frank malignancy, and especially if the growth is of the rapidly growing anaplastic type, the question of treatment by radiotherapy should be considered, as most of these growths recur rapidly after excision and are often very sensitive to radiotherapy. If surgery is decided upon it should be performed with no regard to the facial nerve, this being followed by radiotherapy. In nearly all cases, however, the biopsy will show the tumour to be of the pleomorphic or mixed type, and in this event the parotid gland should be excised by the method described, with preservation of the facial nerve, this formal excision to be followed by radiotherapy.

Summary

A follow-up for six to twenty years is reported in 80 cases of mixed parotid tumours treated by various methods, mainly by conservative excision and some form of radiotherapy.

The tumour recurred in 24 cases, in most instances within one year and only rarely after five years. Seven of these recurrences proved fatal despite further treatment in four of them.

The causes of recurrence are discussed. It is thought that inadequate removal of the tumour is the usual explanation but that some late "recurrences" may represent fresh primary growths.

The more radical type of excision is advocated for mixed parotid tumours as a routine, and a technique is described for the early identification of the trunk of the facial nerve at the stylomastoid foramen to minimize the dangers of injury to the nerve and its branches during the course of the operation.

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PORTAL HYPERTENSION DUE TO EXTRAHEPATIC OBSTRUCTION

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Portal hypertension may be due to intrahepatic or extrahepatic causes. Amongst the latter, the more important recognized aetiological factors may be congenital or acquired stenosis of the portal system of veins; compression by tumours, cysts, or cicatrix; thrombosis due to inflammation or traumatic causes; and, lastly, by what is called cavernomatous transformation of the portal vein. Extrahepatic obstruction of the portal venous system of this nature may produce the syndrome of splenic anaemia with recurrent attacks of haematemesis as its chief symptom. So far, the exact nature and site of the obstruction could not be determined by clinical investigation; only at necropsy, or sometimes at operation, was this possible.

Of the four cases which form the basis of this communication, one was due to obstruction of the splenic vein by a cicatrix over the middle of the anterior surface of the pancreas and two were due to cavernomatous transformation of the portal vein. A fourth case was caused by obstruction of the splenic vein by a pancreatic mass involving the body and tail of the pancreas. In three of these cases the exact diagnosis of the site of obstruction of the portal system of veins was arrived at by splenoportal venography and was later confirmed in the first case at necropsy and in the other two cases at operation.

Case 1

A woman aged 35 was first admitted to hospital with several attacks of haematemesis on August 7, 1953. She had also vomited blood three months prior to this attack. Her past history was not significant. She had no history of abdominal pain or acidity.

The only abnormal findings on admission were severe anaemia and a palpable spleen (two fingerbreadths below the costal margin). She was investigated after her general condition and anaemia had improved. There was no ulcer in the stomach and duodenum on barium-meal examination and no varices could be detected in the oesophagus. Other investigations proved negative. She was discharged, and at this time the spleen was three fingerbreadths below the costal margin. She refused splenectomy. The clinical diagnosis was splenic anaemia with haematemesis.

The patient was readmitted on December 7 with a history of two severe haematemeses on the same day. Physical examination was negative except for evidence of severe haemorrhage and an enlarged spleen, which was just palpable. Hb was 30% and the red-cell count 1,320,000 per c.mm. She was resuscitated by several blood transfusions. The bone marrow showed normoblastic hyperplasia and was otherwise normal. W.R. was negative and thymol turbidity was 10 units. Her anaemia improved with treatment, and the spleen was enlarged to four fingerbreadths below the costal margin and firm in consistency.

She was reinvestigated radiologically. No ulcers were present in the stomach or duodenum, but oesophageal varices were demonstrated. A splenic venogram revealed obstruction of the splenic vein at about its middle and numerous collaterals were seen (Fig. 1). We thought that the haematemeses came from oesophageal varices due to obstruction of the splenic vein, and a splenectomy was decided upon. Just before her transfer to the surgical side she had several bouts of haematemesis and collapsed. Repeated blood transfusions were given to her, but unfortunately she died on February 22, 1954.

A partial post-mortem examination was done. The gross appearances were as follows: Liver was not cirrhotic, but looked slightly fatty and enlarged. The spleen was enlarged

FIG. 1.—Splenic venogram (Case 1) showing obstruction of the splenic vein and upwardly directed collaterals.

FIG. 2.—Photograph of necropsy specimen (Case 1).