- Morgagni, J. B. (1765). *De sedibus et causis morborum per anatomen indagatis*, 2nd ed., 2, p. 33. Remondini, Padua.
- Murray, I. (1952). *British Medical Journal*, 2, 1236.
- Neel, A. (1916). *Hospitalstidende*, 59, 1253.
- (1918). *Ibid.*, 61, 989.
- Nobel, E. (1919). *Wien. klin. Wschr.*, 32, 353.
- Osler, W. (1895). Quoted by Weber (1916).
- Otto, H. (1951). *Nervenarzt*, 22, 68.
- Paramelee, A. H. (1932). *J. Amer. med. Ass.*, 98, 548.
- (1949). *Lipodystrophy*. In Brennenman's *Practice of Pediatrics*, vol. 1, Ch. 41. Prior, Hagerston, Maryland.
- Patton, E. F. (1945). *Amer. J. Dis. Child.*, 70, 31.
- Perutz, A. (1932). *Arch. Derm. Syph. (Wien)*, 166, 653.
- Pic, A., and Gardère, C. (1909). *Lyon méd.*, 113, 61.
- Pollak, F. (1930). *Z. ges. Neurol. Psychiat.*, 127, 415.
- Rasmussen, H. (1933). *Norsk Mag. Lægevid.*, 99, 198.
- Reuben, M. S., Zamkin, H. O., and Fox, H. R. (1924). *Arch. Pediat.*, 41, 480.
- Richardson, J. S. (1946). *Proc. roy. Soc. Med.*, 39, 704.
- Rodriguez Arias, B., and Cuatrecasas, J. (1927). *Arch. Med. Cirug. (Madrid)*, 28, 295.
- Roger, H., Alliez, J., and Paillass, J.-E. (1935). *Rev. franc. Endocr.*, 13, 443.
- Rostowski, J., and McHarg, J. F. (1953). *Edinb. med. J.*, 60, 281.
- Sarbo, A. (1921). Quoted by Serejski (1937).
- Schlau, H. (1929). *Klin. Wschr.*, 8, 1031.
- Schlesinger, A. (1905). *Arch. Kinderheilk.*, 42, 374.
- Schwenke, J. (1922). *Dtsch. med. Wschr.*, 48, 292.
- Serejski, M. (1937). *Wien. klin. Wschr.*, 50, 562.
- Shaw, H. Batty (1905). *Trans. clin. Soc. Lond.*, 38, 222.
- Simons, A. (1911). *Z. ges. Neurol. Psychiat.*, Orig., 5, 29.
- (1913). *Ibid.*, Orig., 19, 377.
- Smith, H. L. (1921). *Johns Hopk. Hosp. Bull.*, 32, 344.
- (1930). *Amer. J. med. Sci.*, 179, 758.
- Spear, I. J. (1918). *Arch. intern. Med.*, 21, 39.
- Sprunt, T. P. (1923a). *Sth. med. J.*, 16, 333.
- (1923b). *Trans. Coll. Phys. Philad.*, 45, 626.
- Strauch, A. (1922). *J. Amer. med. Ass.*, 78, 1037.
- Tixier, L. (1922). *Bull. Soc. Pédiat. Paris*, 20, 352.
- Tizard, J. P. M. (1954). *Proc. roy. Soc. Med.*, 47, 128.
- Tramer, F. (1918). *Msschr. Kinderheilk.*, Orig., 15, 397.
- Trömmner (1923a). *Dtsch. med. Wschr.*, 49, 238.
- (1923b). *Zbl. ges. Neurol. Psychiat.*, 32, 107.
- Warin, R. P., and Ingram, J. T. (1950). *Lancet*, 2, 55.
- Washburn, A. C., and Sanders, U. G. (1932). *Wis. med. J.*, 31, 180.
- Watson, W. N. B., and Ritchie, W. T. (1924). *Quart. J. Med.*, 18, 224.
- Weber, F. Parkes (1913a). *Proc. roy. Soc. Med.*, 6, Neurol. Sect., p. 127.
- (1913b). *British Medical Journal*, 1, 1154.
- (1916). *Quart. J. Med.*, 10, 131.
- (1917). *Brit. J. Child. Dis.*, 14, 179.
- and Bode, O. B. (1930). *Proc. roy. Soc. Med.*, 23, 604.
- and Guncwardene, T. H. (1919). *Brit. J. Child. Dis.*, 16, 89, 200.
- Wertham, F. I. (1929). *Arch. Neurol. Psychiat. (Chicago)*, 22, 714.
- Wilder, J. (1928). *Z. ges. Neurol. Psychiat.*, 116, 275.
- Wilkinson, G. R. (1941). *Sth. Med. Surg.*, 103, 315.
- Williams, M. L., and Kelsey, W. M. (1951). *N.C. med. J.*, 12, 152.
- Wolff, H. G., and Ehrenclou, A. H. (1927). *J. Amer. med. Ass.*, 88, 991.
- Zigler, L. H. (1928). *Brain*, 51, 147.
- and Prout, C. T. (1928). *Amer. J. Psychiat.*, 7, 709.

ACTION OF "ECOLID" IN MAN

BY

F. H. SMIRK, M.D., F.R.C.P., F.R.A.C.P.

Professor of Medicine, University of Otago Medical School,
Dunedin, New Zealand

AND

M. HAMILTON, M.D., M.R.C.P.

Senior Medical Research Officer, Department of Medicine,
University of Otago Medical School, Dunedin, New
Zealand

The pharmacology of methonium salts, in particular pentamethonium and hexamethonium, was described by Paton and Zaimis (1948), and a study of their circulatory action in man was made by Arnold *et al.* (1949). Wien and Mason (1953) described a further series of ganglion-blocking agents, of which one, pentolinium (pentapyrrolidinium, "ansolysen") exhibited stronger hypotensive activity than hexamethonium.

The use of hexamethonium salts in the treatment of hypertensive disorders has been described by Restall and Smirk (1950), Turner (1950), Campbell and Robertson (1950), Smirk (1950), Schroeder (1951), Freis (1951), Smirk and Alstad (1951), Kilpatrick and Smirk (1952), Freis *et al.* (1952), Rosenheim (1952, 1954), McMichael (1952), McQueen and Trewin (1952), Palmer (1952), Freis and Finnerty (1953), Morrison (1953), and Platt (1954).

The use of pentolinium in the treatment of hypertensive states has been described by Smirk (1952, 1953a, 1953b), Maxwell and Campbell (1953), and Freis (1954).

Smirk *et al.* (1954), Freis (1954), and Bain *et al.* (1955) described the effect of combining reserpine with pentolinium. Use of the combination makes it possible to obtain adequate falls in blood pressure with smaller doses of pentolinium, thus gaining a better control over the blood pressure with fewer side-effects.

There remain a number of patients who are made uncomfortable, mainly by the parasympathetic side-effects of pentolinium. Moreover, reserpine has the disadvantage that it may cause mental depression severe enough to require psychiatric treatment. The study of additional ganglion-blocking agents is therefore desirable, and some encouragement is derived from the observation that methonium compounds differ slightly in the relative degrees to which they impair the activities of the sympathetic and the parasympathetic systems.

Studies of the action in man of eclid have been made (Grimson *et al.*, 1955; Smirk and Hamilton, 1955), and a further study is now reported. This substance, although possessing two quaternary nitrogen groupings, differs structurally from hexamethonium and pentolinium (Fig. 1).

Pentapyrrolidinium
(Pentolinium)

Method

Eclid has been administered by subcutaneous injection (in a 2% aqueous solution, and in a 2% solution in 20% polyvinyl pyrrolidone with 0.5% ephedrine) and also

FIG. 1.—Structural formulae of hexamethonium, pentolinium, and eclid.

by mouth. Its action is compared with that of pentolinium. To maintain uniformity with our earlier observations on hexamethonium and pentolinium, the blood pressure was again measured by the method recommended by the Committee for the Standardization of Blood Pressure Readings (1939).

Forty-two patients, all suffering from essential hypertension (two in the malignant phase), have received trial doses of eclid: 23 had received no previous treatment, and 19 had been under treatment previously with pentolinium. Twenty-seven patients received only short courses of treatment with eclid.

Results

Relative Potency of Eclid and Pentolinium

The relative potency of the two drugs varies for each individual. There were 10 patients who showed similar falls in blood pressure following eclid and pentolinium, administered consecutively: in these 10 individuals the dose of eclid was 2.1 times less than that of pentolinium necessary to produce an equivalent hypotensive effect (Table I). Although these comparisons were not made at a uniform

TABLE I.—Potency of Eclid to Pentolinium Needed to Secure Comparable Fall in Blood Pressure

Case No.:	30	297	34	726	970	207	976	990	983	755	Mean
Eclid	1	1	1	1	1	1	1	1	1	1	1
Pentolinium	1.0	2.5	3.6	2.0	2.1	1.8	2.4 (oral)	1.1	2.5	1.9	2.1

time in relation to the start of administration of either drug, it is probable that the figure 2.1 is, if anything, a conservative estimate of the potency of ecolid as compared with pentolinium. The fall in blood pressure shown by 12 previously untreated patients following an initial dose of 1 mg. of ecolid, administered by subcutaneous injection, averaged 51/31 mm. Hg; the fall in blood pressure shown by 12 previously untreated patients following an initial dose of 3 mg. of pentolinium, administered by subcutaneous injection, averaged 61/35 mm. Hg. It therefore seems to be established that, in respect of its action on the blood pressure, ecolid is two to three times more potent than pentolinium, and this ratio is maintained with continued administration.

Comparative Potency of the Parenteral and Oral Preparations of Ecolid

In nine patients it was possible to compare the potency of the parenteral and oral preparations of the compound. In all, the effective oral was far greater than the effective parenteral dose (Table II). From preliminary observations it seems possible that the potency ratio may be dependent upon the ultimate dose of the drug required—those patients requiring a larger effective oral dose showing a high ratio between the parenteral and oral preparations.

TABLE II.—Comparative Potency of Parenteral and Oral Ecolid

Case No.:	30	939	919	17	976	982	703	973	970	Mean
Parenteral ecolid	1	1	1	1	1	1	1	1	1	1
Oral ecolid	8.8	6.3	28.0	26.0	12	17	17	8.5	10	14.8

Course of Fall in Blood Pressure After Ecolid

The duration of the fall in blood pressure after a single dose of ecolid depends upon the extent of that fall, being of longer duration with large falls. In this respect ecolid does not differ from hexamethonium (Morrison and Paton, 1953) or pentolinium (Smirk, 1953a, 1953b). We have attempted to compare the duration of action of drugs when administered in doses which reduce the systolic blood-pressure level in the trough of the blood-pressure fall to 120 mm. Hg (standing posture). Such doses exert a hypotensive effect for at least seven hours with all three preparations of ecolid studied. In a few instances the duration of the fall in blood pressure following a single dose of a 2% solution of ecolid dissolved in 20% polyvinyl pyrrolidone has been between 12 and 13½ hours, and that of the aqueous preparation very little shorter. The preparation in polyvinyl pyrrolidone does not appear to have striking advantages over the 2% aqueous solution.

After subcutaneous injection of the aqueous preparation of ecolid, the blood pressure usually falls to its lowest level

between one and two hours after injection. This trough of the fall in blood pressure occurs slightly later after injection of the preparation dissolved in polyvinyl pyrrolidone, and also when the substance is given orally—namely, one and a half to two hours after administration in each instance.

When a fully effective dose is given parenterally before breakfast, reduction in blood pressure may be maintained without administration of a further dose until the evening. Occasionally a small additional dose is required around lunchtime.

Effect of Ecolid on the Heart Rate

In seven patients the heart rate was unchanged, and in 10 it fell by less than 10 beats a minute, after administration of the drug. The remaining 11 patients showed an increased heart rate, which never exceeded 20 beats a minute in any position (Table III). The change in heart rate bore no relation to the duration of treatment, any one individual showing changes of the same direction and magnitude at the end as at the beginning of a short course of treatment.

TABLE III.—Effect of Ecolid on Postural Change in Blood Pressure and Pulse Rate

Case No.	Before Injection of Ecolid			At "Trough" After Injection of Ecolid		
	B.P. Lying	B.P. Standing	Pulse	B.P. Lying	B.P. Standing	Pulse
207	242/122	224/108	64	204/94	150/88	64
990	188/104	168/90	72	144/82	124/80	76
983	200/126	210/130	84	164/110	160/100	88
703	172/98	160/90	80	156/84	138/64	84
953	252/94	258/94	60	210/92	162/72	60
980	194/92	172/80	88	146/78	142/64	80
968	190/100	200/112	70	162/102	142/94	64
359	204/102	184/90	76	162/88	154/80	72
707	142/100	142/100	84	146/110	122/90	100
747	210/122	190/100	64	164/94	94/58	72
385	228/158	222/170	88	150/76	138/80	76
186	208/124	202/124	72	152/100	150/100	72
732	208/138	208/140	82	182/128	134/102	92
30	234/138	208/132	84	132/92	114/72	76
939	192/120	208/126	84	116/80	98/70	92
797	184/110	180/100	84	128/80	52/72	92
919	184/98	174/94	68	164/92	118/70	64
975	248/148	228/138	88	164/92	140/100	88
17	186/100	160/94	64	150/86	126/60	72
976	176/102	178/102	74	132/80	112/72	74
982	220/130	212/120	72	186/110	162/90	72
726	162/80	182/102	72	120/64	110/64	72
973	224/104	186/96	72	178/88	158/88	68
970	244/146	224/140	88	190/116	156/92	84
34	228/156	238/150	78	146/100	136/106	88
397	258/142	232/138	84	178/112	140/94	76
282	168/110	170/122	64	130/68	128/76	72
755	240/122	180/106	72	172/104	150/86	64

Effect of Posture on the Hypotensive Action

The fall in blood pressure after ecolid is, like that following hexamethonium and pentolinium, greatest when standing, least when lying, and intermediate when sitting.

FIG. 2.—Response of systolic and diastolic blood pressure to a single oral dose of ecolid.

FIG. 3.—Illustrating the additional fall in blood pressure after a meal.

TABLE IV.—*Ratio of Doses Required to Secure Comparable Falls in Blood Pressure on Consecutive Days*

Proportional Increase, in Multiples of the Antecedent Dose													
Case No.	968	359	30	385	732	797	919	17	976	703	34	755	Mean
Parenteral therapy	1.5	3.0	2.0	1.4	1.2	2.3	1.5	1.3	1.7	1.7	2.0	1.5	1.8
Case No.	970	973	703	17	909	Mean							
Oral therapy	1.3	1.2	1.1	1.5	1.4	1.3							

The extent of this postural fall in pressure varies considerably between individuals (Table III), being negligible in five of the 28 patients studied. An example of the usual type of response is illustrated in Fig. 2, which also illustrates the additional effect of meals on the hypotensive action of ecolid.

Effect of Meals on the Hypotensive Action

As with hexamethonium (Smirk and Alstad, 1951) and pentolinium (Smirk, 1953a, 1953b), an additional fall in blood pressure may occur after a meal taken during the course of action of ecolid (Fig. 3). This postprandial fall occurs within one hour of the meal in every instance, but bears no other constant relationship to food.

In four of the patients the trough of the fall in blood pressure did not occur until after lunch: although all four showed some fall in pressure initially, the postprandial exceeded the post-injection fall in blood pressure (Fig. 3).

Toleration

There is no doubt that individuals become tolerant to both the oral and the parenteral preparations of ecolid, as shown by the necessity for increases in dose during the early stages of treatment. In the first few days of administration it has been noted that in order to reproduce a fall in blood pressure on consecutive days the dose must be almost doubled (Table IV): conversely, administration of the same dose on consecutive days leads to a halving of hypotensive effect (Table V). To maintain falls in blood

TABLE V.—*Reduction in Fall in Blood Pressure with Administration of the Same Dose on Consecutive Days*

Case No.	968	939	17	976	34	970	Mean
Reduction %	31	45	63	82	12	37	45

TABLE VI.—*Dose of Ecolid at Beginning and End of a Short Period of Administration, in Relation to Duration of Administration*

Case No.:	359	30	973	953	968	385	732	797	982	34	282	983	726	919	976	970	990	17	980	392	207	703	755
Parenteral:																							
Duration (days) ..	2	2	2	3	3	3	3	3	3	3	3	4	4	6	6	7	9	9	20	21	46	62	69
Dose (mg.) at start ..	1	1	1	1.5	1	1.7	2	2	2	1	2.6	1	1	2	1	1.5	2.0	2	2.0	0.5	2.6	0.6	2
Dose (mg.) at end ..	3	2	2	5	2	3	5	8	3	4	2.0	2.8	2	5	3.6	3.2	4.3	5.4	5.6	4.6	11.4	5.2	14
Oral:																							
Duration (days) ..		2												8	3			5			53	48	
Dose at start ..		10												44	3.6			60			125	15	
" " end ..		14												220	50			180			425	72.5	

TABLE VIII.—*Summary of 15 Patients Treated by a Prolonged Course of Ecolid*

Case No.	Age	Sex	Retinal Grade	Complication of Disease	Daily Dose (mg.) Ecolid		No. of Doses a Day	Degree of Control	Side-effects	Duration of Treatment
					Parenteral	Oral				
110	49	F	3	None		600	2	Good	None	4 months
207	61	M	4	"		300	3	"	"	4 " *
1001	54	M	2	Angina		300	2	"	Visual blurring	4 " "
703	50	F	2	Myocardial infarction		120	2	"	None	6 " "
1003	52	F	1	None		375	2	Fair	Constipation	3 " "
755	48	M	4	"	14.8	450	2	Good	Diarrhoea, Blurred vision	8 " "
912	60	M	4	Heart failure	6.0		2	"	Constipation	4 " *
1000	61	M	2	None	5.6		2	Fair	"	2 " *
1019	58	M	2	Heart failure		350	2	"	None	3 " "
713	50	M	4	Malignant hypertension	32		3	Good	"	1 " "
392	52	F	2	Heart failure		600	2	Poor	Constipation, Stomatitis	1 " †
1036	65	F	2	Angina		75	2	Good	None	1 " "
1039	60	M	2	"		400		"	"	6 weeks
1034	65	M	2	None	30	450	2	"	Blurred vision, Constipation	1 month
1035	62	M	4	Malignant hypertension	10		2	"	Constipation	6 weeks*

* Patient also receiving reserpine.

† Patient discontinued treatment, as result of severe ulceration of mouth, following excellent response of heart failure to the therapy.

pressure the dose must be increased daily during the first few days of administration while toleration is developing rapidly. The daily increments necessary vary from individual to individual (Table VI).

Cross-toleration Between Ecolid and Pentolinium

Evidence for the existence of cross-toleration between hexamethonium and pentolinium has been presented by Smirk (1953a, 1953b). We have found a similar state of cross-toleration to exist between ecolid and pentolinium, in that the initial effective dose of ecolid is greater in patients previously treated with pentolinium than in those who have received no previous treatment. In 12 previously untreated patients the mean reduction in blood pressure from 1 mg. of the aqueous preparation, given by subcutaneous injection, was 51/32 mm. Hg, whereas in 11 patients previously treated with pentolinium the mean reduction was 36/18 mm. Hg from a 2-mg. dose of the same preparation (Table VII).

TABLE VII.—*Mean and Range of Falls in Blood Pressure Obtained from the First Dose of Ecolid in Patients Previously Treated with Pentolinium, Compared with Those Who Were Previously Untreated*

	Initial Dose of Ecolid	No. of Patients	Fall in B.P.	
			Mean	Range
No previous pentolinium ..	1 mg.	12	51/32	26/16–102/48
Previous pentolinium ..	2 "	11	36/18	6'8 –104/62

The response to the first dose of pentolinium was observed in a group of patients who had received preliminary treatment with ecolid. All showed a smaller fall in blood pressure from the initial dose of pentolinium than would be expected in an untreated case.

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.

Acknowledgment is made to Miss N. Richardson for secretarial assistance, to the Otago Hospital Board for helpful co-operation, to Ciba Ltd. for supplies of ecolid, and to May and Baker Ltd.

for supplies of pentolinium (ansolysen). Expenses have been defrayed in part by the Medical Research Council of New Zealand.

REFERENCES

- Arnold, P., Goetz, R. H., and Rosenheim, M. L. (1949). *Lancet*, **2**, 408.
 Bain, C. W. C., Ashton, F., and Jones, B. P. (1955). *British Medical Journal*, **1**, 817.
 Campbell, A., and Robertson, E. (1950). *Ibid.*, **2**, 804.
 Committee for Standardization of Blood Pressure Readings: American Heart Association and Cardiac Society of Great Britain and Ireland (1939). *Brit. Heart J.*, **1**, 261; *J. Amer. med. Ass.*, **113**, 294.
 Freis, E. D. (1951). *Med. Ann. Distr. Columbia*, **20**, 297.
 — (1954). *Med. clin. N. Amer.*, **38**, 363.
 — and Finnerty, F. A., jun. (1953). *G.P. (Kansas)*, **7**, No. 3, p. 71.
 — Schnaper, H. W., and Johnson, R. L. (1952). *Circulation*, **5**, 20.
 Grimson, E. S., Tarazi, A. K., and Frazer, J. W., jun. (1955). *Ibid.*, **11**, 733.
 Kilpatrick, J. A., and Smirk, F. H. (1952). *Lancet*, **1**, 8.
 McMichael, J. (1952). *British Medical Journal*, **1**, 933.
 McQueen, E. G., and Trewin, E. (1952). *Med. J. Aust.*, **2**, 425.
 Maxwell, R. D. H., and Campbell, A. J. M. (1953). *Lancet*, **1**, 455.
 Morrison, B. (1953). *British Medical Journal*, **1**, 1291.
 — and Paton, W. D. M. (1953). *Ibid.*, **1**, 1299.
 Palmer, A. J. (1952). *Med. J. Aust.*, **2**, 428.
 Paton, W. D. M., and Zaimis, E. J. (1948). *Nature (Lond.)*, **162**, 810.
 Platt, R. (1954). *Quart. J. Med.*, **23**, 441.
 Restall, P. A., and Smirk, F. H. (1950). *N.Z. med. J.*, **49**, 206.
 Rosenheim, M. L. (1952). *Proc. roy. Soc. Med.*, **45**, 269.
 — (1954). *British Medical Journal*, **2**, 1181.
 Schroeder, H. A. (1951). *Amer. J. Med.*, **10**, 189.
 Smirk, F. H. (1950). *Lancet*, **2**, 477.
 — (1952). *Proc. Univ. Otago med. Sch.*, **30**, 13.
 — (1953a). *Lancet*, **1**, 457.
 — (1953b). *N.Z. med. J.*, **52**, 325.
 — and Alstad, K. S. (1951). *British Medical Journal*, **1**, 1217.
 — Doyle, A. E., and McQueen, E. G. (1954). *Lancet*, **2**, 159.
 — and Hamilton, M. (1955). *Proc. Univ. Otago med. Sch.*, **33**, 11.
 Turner, R. (1950). *Lancet*, **2**, 353.
 Wien, R., and Mason, D. F. J. (1953). *Ibid.*, **1**, 454.

TREATMENT OF MIXED PAROTID TUMOURS

BY

F. G. SMIDDY, M.B., F.R.C.S.

Tutor in the Department of Surgery, General Infirmary at Leeds

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