Conclusion

The incomputable factor in cancer prognosis! I make no boastful claim for surgical responsibility for those "successes" which I have ventured to place before you: many causal factors are concerned, not least the innate resisting power of the individual patient to cancer invasion. Sir James Barrie tells us somewhere that God gave us memory "that we might have roses in December." Those patients to whom I have referred are some of my "roses in December." I have wanted to share my roses with you. They are my sources of encouragement in the cancer fight: they are an earnest of the coming of "the rose-fingered dawn," when for the cure of cancer gross mechanical destruction and cruel mutilation of tissues shall perhaps no longer be required, nor the scorching methods and machinery of Hephaestus, the blacksmith god, or of Prometheus, who stole fire from heaven.

I will conclude with this message of confidence that was employed by Sir Alfred Pearce Gould in the closing sentence of his Bradshaw Lecture in 1910, and in the *ipsissima verba* of my old master: "We are apt to envy the astronomers who know so well the movements of the spheres, that they foretell the happenings of the universe with a precision that is the despair of workers in other branches of natural science. But with all their knowledge of these laws they cannot hasten on the day, or affect in one small circumstance the movement of a planet, or alter the destiny of a single grain of meteoric dust. But when the biologist shall know the laws that govern cell-growth, with a knowledge akin in its sweep and accuracy to that of the astronomer, he will have power, and that power will enable him to prevent, to control, and to cure cancer."

Research has taught us that that power is not so far distant from our grasp to-day.

REFERENCES

- Allen, A. C. (1949). *Cancer*, 2, 28.
 Banks, W. Mitchell (1878). *Liverpool and Manchester Medical and Surgical Reports*, p. 192.
 — (1893). *The Gentle Doctor*. Lee and Nightingale, Liverpool.
 Bowlby, Sir Anthony (1925). *Brit. med. J.*, 1, 234.
Brit. med. J., 1954, 2, 1234.
 Broster, L. R. (1923). *Brit. J. Surg.*, 11, 287.
 — (1930). *Proc. roy. Soc. Med.*, 23, 551.
 Bryant, T. (1902). *Brit. med. J.*, 1, 1200.
 Cade, Sir Stanford, and Lee, E. S. (1957). *Brit. J. Surg.*, 44, 433.
 Cairns, F. D. (1922). *Ibid.*, 10, 290.
 Clifton, J. A., Philipp, R. J., Ludovic, E., and Fowler, W. M. (1952). *Amer. J. med. Sci.*, 224, 121.
 Cole, W. H., Roberts, S., Watne, A., McDonald, G., and McGrew, E. (1958). *Bull. N.Y. Acad. Med.*, 34, 163.
 Dawson, H. G. W. (1922). *Brit. med. J.*, 2, 757.
 Elsberg, C. A. (1928). *Surg. Gynec. Obstet.*, 46, 1.
 Engell, H. C. (1955). *Acta chir. scand.*, Suppl. 201.
 Franks, L. M. (1954). *Ann. roy. Coll. Surg. Engl.*, 15, 236.
 — (1956a). *Lancet*, 2, 1037.
 — (1956b). *J. Path. Bact.*, 72, 603.
 Gillies, Sir Harold (1949). *Proc. roy. Soc. Med.*, 42, 176.
 Gordon-Taylor, Sir Gordon (1938). *Brit. med. J.*, 2, 1071.
 — (1948). *Ann. roy. Coll. Surg. Engl.*, 2, 60.
 Gould, A. P. (1882). *Trans. med. Soc. Lond.*, 6, 177; *Lancet*, 1, 560.
 — (1892). *Lancet*, 1, 411.
 — (1910). *Ibid.*, 2, 1665.
 Hadfield, G. (1954). *Brit. med. J.*, 2, 607.
 Heath, C. (1871). *Lancet*, 1, 847.
 — (1898). *Brit. med. J.*, 2, 1783.
 His, W. (1870). *Arch. mikr. Anat.*, 6, 229.
 Kettle, E. H. (1912). *J. Path. Bact.*, 17, 40.
 Lloyd-Davies, O. V. (1957). *Brit. J. Surg.*, 45, 113.
 McClure, J. (1936). *Lancet*, 2, 371.
 Manson, J. S. (1922). *Brit. med. J.*, 1, 996.
 — (1925). *Ibid.*, 1, 234.
 Moore, C. H. (1867). *Med.-Chir. Trans.*, 50, 245.
 Mori, T. (1913). *Frankfurt. Z. Path.*, 12, 2.
 Newcomb, W. D. (1936). *Proc. roy. Soc. Med.*, 30, 113.
 Nicholson, G. W. (1923). *Guy's Hosp. Rep.*, 73, 164.
 Papanicolaou, G. N. (1954). *Atlas of Exfoliative Cytology*. Harvard Univ. Press, Cambridge, Mass.
 Pringle, J. H. (1937). *Lancet*, 1, 508.
 Raeburn, C., and Spencer, H. (1953). *Thorax*, 8, 1.
 Riches, E. W. (1958). *Trans. med. Soc. Lond.*, 74, 132.
 Rickham, P. P. (1957). *Brit. J. Surg.*, 44, 492.
 Roberts, S., Watne, A., McGrath, R., McGrew, E., and Cole, W. H. (1958). *A.M.A. Arch. Surg.*, 76, 334.
 Steward, F. J. (1925). *Brit. med. J.*, 1, 156.
 Sumner, W. C. (1953). *Cancer*, 6, 1040.
 Trinkle, A. J. (1936). *Amer. J. Cancer*, 27, 676.
 Verneuil (1888). *Sem. méd. (Paris)*, 8, 112.
 Webb-Johnson, A., and Macleod, C. E. A. (1924). *Brit. med. J.*, 1, 314.
 Wilbur, D. L., and Hartman, H. R. (1931). *Ann. intern. Med.*, 5, 201.
 Wilder, W. H. (1900). *J. Amer. med. Ass.*, 35, 1363.
 Willis, R. A. (1953). *Pathology of Tumours*, 2nd ed. Butterworth, London.

TREATMENT OF HYPERTENSION WITH PENTOLINUM AND MECAMYLAMINE

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Ganglion-blocking agents are now recognized as being the treatment of choice for the more severe forms of hypertension. The ideal ganglion-blocking agent has yet to be found, and in the meantime there is a temptation to turn too readily to each new preparation as it appears, without properly evaluating its predecessors.

At the present time, therefore, when new ganglion-blocking agents are continually being put at our disposal, two of which are currently being used in this department, it seemed worth while to consider what measure of long-term control could be obtained by means of pentolinum and mecamlamine, both of which have now been widely used. The present paper is based on our experience of these drugs in the treatment of 78 patients with severe hypertension between April, 1954, and May, 1958.

Selection of Patients

Of the 78 patients in the present series, 47 were judged to have malignant hypertension from the level of the diastolic blood pressure and the presence of papilloedema. The remaining 31 all had severe benign hypertension with diastolic pressures over 120 mm. Hg and lesser grades of retinopathy. Several of these patients were probably in a pre-malignant phase in view of the progressive retinopathy. We wish to emphasize that we have not included patients with mild benign hypertension and a diastolic pressure below 120 mm. Hg in this series. All patients with these criteria were treated with ganglion-blocking agents unless some contraindication to treatment was present. A raised blood urea, recent cardiac or cerebral thrombosis, and severe cerebral arteriosclerosis were all considered to be partial but not absolute contraindications. Each patient was judged on his or her

merits, and even those with limited life expectancy were treated if sight was deteriorating. The age range of patients varied from 15 to 65 years, average 44.7 years; 46 were males, and 32 females. The aetiology of the hypertension was varied; a number with pre-existing renal disease are included.

Use of Reserpine

It is well recognized that reserpine, in addition to exerting a mild hypotensive effect in 41% of patients when used alone (Platt and Sears, 1956), is similarly useful in conjunction with a ganglion-blocking agent. In this way it is often possible to achieve a satisfactory blood-pressure level with a lower dose of the blocking agent and hence fewer side-effects. It has therefore been our standard practice to use both types of treatment whenever possible. In order to avoid subsequent interference with stabilization from the delayed effect of reserpine, we consider that, when possible, treatment with the latter should be started immediately the patient is seen in the out-patient clinic. In this way it will be apparent by the time of admission either that reserpine is having no effect, in which case it is discontinued, or that it is already exerting its usual hypotensive effect, to which the ganglion-blocking agent is added. In exceptional patients, not included in this study, reserpine alone was adequate to control even severe hypertension. In patients with malignant hypertension in whom the sight is threatened, it is unjustifiable to delay treatment with pentolinium or mecamlamine, and in these circumstances reserpine was started simultaneously with the ganglion-blocking agent.

In-patient Stabilization

All patients in this series were admitted to hospital for initial stabilization. On the assumption that the urgency of the symptoms did not necessitate immediate treatment the patient was allowed a few days on reserpine alone, in order to provide a baseline for the blood-pressure readings. During this period no attempt was made to enforce bed rest, unless it was necessary on other counts. After a satisfactory baseline had been obtained, the ganglion-blocking agent was started. In the case of pentolinium, the usual starting dose for uncomplicated patients was 20 mg. four times a day, 20 to 30 minutes before the main meals—that is, at 7.30 a.m., 12.30 p.m., 5.30 p.m., and 10.30 p.m. We consider that this constant time relation to meals is important in ensuring a consistent rate of absorption. If accumulation of the drug due to renal impairment seemed likely, twice daily dosage, at 7.30 a.m. and 5.30 p.m., was used. Mecamlamine was usually given orally twice daily, at 7.30 a.m. and 5.30 p.m., in the first instance, starting at 5 mg. a dose.

Thereafter, in either case, the blood pressure was taken lying and standing, each day at the same time, which as a matter of convenience was arbitrarily fixed at 10.30 a.m. The dose was steadily increased at daily intervals, or less often as determined by the blood-pressure response and the possibility of retention owing to impaired renal function, until a hypotensive effect was obtained. The blood pressure was then recorded hourly on one or more days. In this way the duration of action of a single dose was assessed, and the frequency of administration necessary to achieve a continuous hypotensive response determined. This

response was reassessed as often as necessary until a satisfactory result was obtained.

It was found that in most cases three or four doses of pentolinium were required daily, but only two or three of mecamlamine. Some patients with renal impairment might be controlled on one dose a day, or even every other day. The total daily dose was usually evenly divided between the individual doses, but it was sometimes necessary to give more at one time of day than at another.

Out-patient Supervision

All patients were seen, at intervals of one to four weeks after discharge from hospital, by one of us (H. T. N. S.) in a clinic exclusively concerned with the management of hypertensive patients. Whenever possible an attempt was made to see the patient at the same time of day on each visit. At these interviews the blood pressure was taken three times, both lying and standing, and the lowest reading in each posture was recorded. The dose was adjusted according to the blood-pressure response and the occurrence of any side-effects. The patient was thereafter seen at intervals as necessary.

One of the most important points emerging from the out-patient supervision of our hypertensive patients was the necessity for frequent, often minor, alterations in the regime in order to control side-effects, while maintaining effective levels of dosage. Intelligent co-operation on the part of the patients was found to facilitate control of treatment, and, by contrast, in an unintelligent patient control was more difficult and less satisfactory. Adequate time for interviews was important and in a three-hour session it proved impracticable to see more than 12 patients.

Dosage and Tolerance

There was considerable individual variation in tolerance to these drugs, as reflected in the range of dosage employed, which with pentolinium ranged between 20 and 640 mg. a day, and with mecamlamine between 2.5 mg. every third day, and 80 mg. daily. In the case of pentolinium alteration in the completeness of absorption from patient to patient, and from time to time in the same patient, undoubtedly accounted for some of the changes; but since a similar, though less marked, phenomenon was noticed with mecamlamine, which is more or less completely absorbed, some variation of tolerance must be postulated. This usually necessitated a gradual increase of dosage, but occasionally the reverse was true.

Results

Of the 78 patients treated, 40 were given pentolinium and 25 mecamlamine; the other 13 were given both forms of treatment at different times. In regard to these 13 we have included (see Chart) only that fall in diastolic pressure recorded during treatment with the more effective of the two drugs. The initial diastolic pressure was taken as the mean of several in-patient readings—these usually being distinctly lower than those obtained in the out-patient department—and ranged between 120 and 220 mm., with a mean of 145 mm. Hg (median 145 mm.). No attempt has been made to indicate the accompanying fall in systolic pressure, which was more variable and often seemed unrelated to the severity of the disease.

Survival Rate

Since it is impossible to arrive at any accurate estimate of life expectancy in untreated benign hypertension, the effect of ganglion-blocking agents on survival has been considered only in relation to the 47 patients with malignant hypertension, in which condition a fairly clear-cut prognosis exists in the

untreated state. Both pentolinium and mecamylamine had similar effects on the diastolic pressure, and it seemed unlikely that there could be any significant difference between the two on the survival rate. For this reason, and since the number of patients available was small, no attempt has been made to compare the effect of the two preparations in this respect.

Of the 47 patients, 13 died, 8 (62%) within the first six months of treatment. Most of them were patients with already advanced disease in whom treatment was instituted too late to prevent irreversible damage.

After the first six months, the death rate was much lower and the Table shows the survival rates for our patients compared with those for untreated patients reported by Keith *et al.* (1939) and Kincaid-Smith *et al.* (1958). The number of patients observed is too small to justify statistical analysis of the survival rate, and some anomalies are apparent, such as the 95% survival in the small group observed for 24 months.

Retinopathy

With two exceptions (one patient in whom the blood pressure was never effectively controlled and another

who had a blood urea of 188 mg. per 100 ml. at the start of treatment and died four months later) all patients with severe hypertensive retinopathy showed marked improvement. In all patients with papilloedema this resolved in from two to four months, there being in these and other patients a corresponding decrease or disappearance of exudates and haemorrhages. In most patients, including those originally with papilloedema, the only residual abnormalities were variation in the calibre of the retinal arteries and "nipping" of the veins at the arterial crossings.

Side-effects and Complications

One of the most important limiting factors in the use of ganglion-blocking agents is the presence of side-effects, most of which are due to the unwanted suppression of parasympathetic activity. The most common complaints in order of frequency were constipation, dryness of the mouth, paralysis of accommodation, hesitancy of micturition, and occasionally impotence.

On the whole, side-effects were more noticeable with mecamylamine than with pentolinium. Constipation was disproportionately severe with mecamylamine, and in one patient led to paralytic ileus with intestinal obstruction. Paralytic ileus due to mecamylamine, presenting as a surgical emergency, has also been reported by Grant and Boyd (1957).

In this connexion it is interesting to note that Bennet *et al.* (1957) emphasized that mecamylamine has other actions than those of a ganglion-blocking agent, including a direct post-ganglionic depressant effect on the contraction of intestinal muscle. They suggest that this is the reason for the unduly high incidence of intestinal side-effects with mecamylamine.

Another hazard of constipation was the sudden development of profound hypotension, presumably due to the more complete absorption of the drug consequent upon the intestinal stasis. The fact that this complication occurred in our experience only with pentolinium is in conformity with the view that mecamylamine is completely absorbed under normal conditions.

Because of the dangers, as well as the discomforts of constipation, brought about by these agents, we pay particular attention to measures designed to counteract it. These include "All Bran" for breakfast, and when necessary a standardized senna preparation at night; but if, despite such steps, constipation continued, we often thought it wiser to reduce the dose of ganglion-blocking agents temporarily than to run the risk of the complications mentioned.

In addition to the side-effects common to all ganglion-blocking agents, mecamylamine was found to possess two other effects, apparently peculiar to itself. One was the development of a coarse tremor, which we observed in two patients. In the first of these, its significance not being immediately realized, mecamylamine administration was continued for a short time and led to the development of a psychotic state. The patient, a 35-year-old man, was suffering from chronic renal disease and hypertension. Despite a blood urea of 156 mg. per 100 ml., it was decided to start treatment with mecamylamine in view of the severe retinopathy. The dose was gradually increased to 45 mg. daily, by which time he noticed a coarse tremor of the hands, which became worse over the next

Comparison of Survival Rates

Period of Observation up to Closure of Series	*No. at Risk	No. Surviving at Stated Interval after Starting Treatment	Survival Rate		
			Present Series	Keith <i>et al.</i> (1939)	Kincaid-Smith <i>et al.</i> (1958)
6 months	42	36	86%	46%	20%
12 "	37	30	81%	21%	10%
18 "	26	23	88%	13%	6%
24 "	21	20	95%	12%	5%
30 "	12	10	83%	8%	4%

*The "number at risk" for each period of observation includes all patients who either have been observed for that period or could have been had they lived; it excludes patients entering the series too recently for this period of observation to have been completed. For instance, a patient entering the series—that is, beginning treatment—15 months before it was closed, whether now alive or dead, is considered as "at risk" in the follow-up at 6 and 12 months but not for the longer periods of observation.

few days. On the fourth day he became confused and hallucinated, the clinical picture being that of delirium tremens. Mecamylamine was stopped, but the tremor and psychosis persisted for 10 days before recovering.

A second patient, a 49-year-old man, developed a coarse tremor and mental confusion while receiving 80 mg. of mecamylamine daily. In this patient the blood urea was 78 mg. per 100 ml., and here again the symptoms cleared up on stopping mecamylamine.

Similar effects have been noted by others (Doyle and Neilson, 1956; Schneckloth *et al.*, 1956; Deming *et al.*, 1957; Harington and Kincaid-Smith, 1958), and a suggestion has been made that the tremor is due to the associated uraemia (Greenberg and Davidson, 1958).

We do not think that the tremor in our patients resembled the twitching which occurs in some uraemic patients, usually with very high levels of blood urea, and we are convinced that both the tremor and the psychosis were due to the mecamylamine. In support of this contention Schneckloth *et al.* (1956) noted that of their seven patients showing these effects only four were notably uraemic. The other three had blood ureas of 27 mg., 45 mg., and 50 mg. per 100 ml. respectively.

A second side-effect of mecamylamine, the complaint of feeling "drugged" while receiving therapeutic doses, is perhaps even more important because of its ubiquity. Smirk and McQueen (1957) also noted this side-effect with mecamylamine, although not with pentolinium, but did not emphasize its importance. In our experience, this lack of well-being was the commonest complaint of patients taking mecamylamine and materially added to their discomfort. It was one of our main reasons for changing to an alternative preparation.

Discussion

There is no doubt that both pentolinium and mecamylamine are potent hypotensive agents. We are not, however, here concerned merely with their effect on the blood pressure, but with the no less important effects on the patient as a whole and their suitability for long-term use. In this respect so much depends on the patient's subjective impressions that blood-pressure figures alone are totally inadequate, and we have therefore been forced to rely in part on clinical impressions.

It should be made clear that whilst we have tried to achieve a satisfactory drop in blood pressure we have not, except in a few patients, aimed at normal levels. The conversion of a symptom-free patient with a dangerously high blood pressure to one with reasonably normal levels but severe side-effects is a common experience, and one which we tried to avoid by aiming at a more modest reduction in blood pressure to relieve any symptoms originally present, without substituting others caused by the treatment. Our results must therefore be considered in the light of these views, for the figures do not represent the lowest levels which could be obtained, but rather the optimum lowering commensurate with well-being. With relatively short-acting preparations such as mecamylamine and pentolinium it is difficult to obtain a satisfactory continuous lowering of the blood pressure, but even with the relatively imperfect control at present obtainable without imposing too many restrictions on the patient it is gratifying and perhaps surprising that the severe retinopathy, including papilloedema, is so much improved as a result of treatment.

The most important yardstick by which to assess improvement is survival. Between 79% (Keith *et al.*, 1939) and 90% (Kincaid-Smith *et al.*, 1958) of untreated cases of malignant hypertension end fatally within a year; by comparison 81% of our cases were alive one year after treatment started. Smirk (1954) reported that 75% of patients with malignant hypertension were alive after 18 months' treatment with hexamethonium, and our figure is very similar. Six of our patients are still under treatment after at least four years.

On the debit side both pentolinium and mecamylamine require careful stabilization and continual time-consuming supervision in order to obtain and maintain a satisfactory depression of blood pressure, which even at best still fluctuates fairly widely. In addition to these difficulties of control were the side-effects already mentioned, which were most marked with mecamylamine. All those patients who had experience of both pentolinium and mecamylamine preferred the former, and we have now stopped using mecamylamine.

We conclude, therefore, that in our experience both pentolinium and mecamylamine are powerful hypotensive agents capable of saving sight and prolonging life. Both have their imperfections; but, of the two, pentolinium is to be preferred as having fewer and less severe side-effects, enabling the patient to live a relatively normal life. Whether one of the newer ganglion-blocking agents will eventually supplant pentolinium only further experience will show.

Summary

We describe our experiences in the control of 78 severely hypertensive patients with pentolinium and mecamylamine extending over four years. Side-effects, which occur with both preparations, were more numerous and severe in the case of mecamylamine; in our opinion this outweighed the advantage of its more constant absorption and rendered it unsuitable for long-term use. In some patients the synergistic effect of reserpine enabled the dose of ganglion-blocking agents to be reduced, with a concomitant decrease in the severity of side-effects. Despite the shortcomings of both preparations the results achieved have been most gratifying as regards both the prolongation of life and the restoration and preservation of sight. New ganglion-blocking agents are now available which, from a short acquaintance, seem to offer certain advantages over the older preparations, but it remains to be seen whether they will stand the test of long-term use or be able to improve significantly upon the results already obtained.

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REFERENCES

- Bennet, G., Tyler, C., and Zaimis, E. (1957). *Lancet*, 2, 218.
- Deming, Q. B., Hodes, M. E., Edreira, J. G., and Baltazar, A. (1957). *New Engl. med. J.*, 256, 739.
- Doyle, A. E., and Neilson, G. H. (1956). *Brit. med. J.*, 2, 1431.
- Grant, A. P., and Boyd, J. S. (1957). *Lancet*, 1, 713.
- Greenberg, M., and Davidson, E. (1958). *Ibid.*, 1, 641.
- Harington, M., and Kincaid-Smith, P. (1958). *Ibid.*, 1, 499.
- Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, 197, 332.
- Kincaid-Smith, P., McMichael, J., and Murphy, E. A. (1958). *Quart. J. Med.*, 27, 117.
- Platt, R., and Sears, H. T. N. (1956). *Lancet*, 1, 401.
- Schneckloth, R. E., Corcoran, A. C., Dustan, H. P., and Page, I. H. (1956). *J. Amer. med. Ass.*, 162, 868.
- Smirk, F. H. (1954). *Brit. med. J.*, 1, 717.
- and McQueen, E. G. (1957). *Ibid.*, 1, 422.