Treatment of Hypertension with Methyldopa

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In recent years there has been a progressive improvement in the agents available for lowering blood-pressure. In the majority of cases high blood-pressure can now be reduced to normal levels, though not always wisely or without side-effects.

Previous reports have agreed that methyldopa has advantages over other drugs in being relatively free from severe side-effects, though these in some degree are experienced by most patients and some have to stop treatment altogether on this account. In many, also, it has not been possible to maintain adequate control over the blood-pressure.

We feel there is now a place for a fairly definitive statement based on a large group of patients studied over a sufficient period of time to draw long-term conclusions. This paper describes our experience with methyldopa in the treatment of 114 patients. Fourteen of these had to discontinue treatment after less than six months. The remaining 100 were treated for periods of 6 to 36 months, and details are also given of a preliminary double-blind trial carried out on a small number of patients.

Material and Methods

The 100 patients (37 males, 63 females) in this series who completed six months' treatment were aged from 29 to 77, with an average of 54 years. The duration of follow-up is shown in Table I.

TABLE I.—Duration of Follow-up

6-11 months	..	..	100 cases
12-17 "	..	..	79 "
18-23 "	..	..	42 "
24-29 "	..	..	21 "
30-36 "	..	..	3 "
Average period of follow-up, 15.7 months.			

The majority of patients, including all those with evidence of hypertensive disease, were first admitted to the ward in order to exclude any important underlying condition for which special treatment might be required, to assess the need for treatment, and, in such cases, to establish a satisfactory regime which could then be continued at home under the care of the general practitioner in conjunction with the hospital clinic. A few in the relatively mild group were first assessed on an out-patient basis.

Clinical Features

The clinical features of these patients are summarized in Table II, where a preliminary subdivision into group A, the more severely disabled cases, and group B, those rather less severely disabled, has been made. Criteria for inclusion in either group are shown in Table II.

Group A (42 cases) comprised those who in addition to high resting diastolic pressures (120 mm. or over) had hypertensive

retinopathy or unequivocal electrocardiographic evidence of left ventricular hypertrophy, as defined below, or both.

The 58 patients in group B were cases of lesser severity, but almost all, in addition to raised resting diastolic pressures (105 mm. or over), had hypertensive arteriolar changes in the fundi, and 14 also showed electrocardiographic evidence of left ventricular hypertrophy.

TABLE II.—Clinical Features

	Group A (42)	Group B (58)	Total (100)
Mode of presentation	Left ventricular failure	3	4
	Cerebrovascular accident	10	8
	Headache	6	9
	Visual disturbance ..	4	5
	Routine examination ..	10	19
	Miscellaneous	9	13
Renal function	Normal	29	53
	Impaired	8	3
	Renal failure	5	2
Left ventricular hypertrophy (E.C.G.)	Present	35	14
	Absent	7	44
Retinal changes	Grade I	5	27
	" II	12	27
	" III	21	3
	" IV	4	1
Resting diastolic pressure before treatment	105-129	19	48
	130-149	21	9
	150+	2	1

Retinal changes were classified according to the criteria recommended by Keith, Wagener, and Barker (1939) after detailed examination by an ophthalmologist.

Criteria for left ventricular hypertrophy based on data given by Simonson (1961). Renal failure denotes a blood-urea level persistently above 40 mm./100 ml. Impaired renal function denotes an endogenous creatinine clearance below 100 litres/24 hours and/or phenolsulphonphthalein excretion below 20% in 15 minutes.

The group of 22 patients with miscellaneous presentation includes those referred to the out-patient clinic with unrelated disease but found on examination to be hypertensive.

Drug Regime

Methyldopa, 250 mg. two or three times a day, was the initial dose, and this was increased by increments of 250 mg. at intervals of four to seven days until the desired fall in blood-pressure had been obtained, or until it became clear that the addition of an oral diuretic would be necessary. The average dose used in the whole group of 100 patients was 1,300 mg., with a range of 500 to 3,000 mg. daily. The average for the more severely disabled group A patients was 1,400 mg. daily, as against 1,200 mg. daily among the less-disabled group B patients.

Chlorthalidone was added to the drug regime in 34 cases. The usual dose was 50 mg. daily, but in four patients 100 mg. daily was given. This oral diuretic was prescribed for the following reasons: (1) to overcome tolerance, (2) to permit the use of a smaller dose of methyldopa where side-effects were prominent, (3) where fluid retention occurred, and (4) occasionally to achieve rapid control over blood-pressure in patients with severe manifestations such as papilloedema or pulmonary oedema.

Nearly two-thirds of the patients in this series had previously been treated with other antihypertensive drugs and were trans-

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ferred to methyldopa when pressure control was unsatisfactory or when side-effects were unacceptable.

Hypertensive Clinic

Patients attended the clinic for a period of two to three hours at intervals of one to three months, and were interviewed by physicians. Lying and standing pressures were recorded by a technician at hourly intervals for two or three hours at each visit, and the average of these readings has been taken in assessing all results. In certain patients pressures were also recorded after they had hurried up a flight of stairs so that the effect of exercise could be assessed. All blood-pressure were recorded on the right arm after the fourth consecutive inflation of the cuff.

Results

The preliminary double-blind trial involving 11 patients established the efficacy of methyldopa in producing a reduction in blood-pressure. The fall averaged 20/10 mm. Hg in the lying position and 26/17 mm. Hg in the standing position. These results were highly significant ($P < 0.001$).

Classified Results

In classifying our results the following criteria have been used: (1) A reduction in diastolic pressure of 40 mm. Hg or a standing diastolic pressure below 100 mm. Hg constitutes a good result; (2) a reduction in diastolic pressure of 30 mm. Hg or a reduction of standing diastolic pressure below 110 mm. Hg denotes a fair result. Any result less than these has been classified as poor.

By these criteria, and considering only the reduction in blood-pressure, the 100 patients showed the results given in Table III.

TABLE III.—Classified Blood-pressure Responses in 100 Cases

	Group A (Severe)	Group B (Mild)	All Cases
Good result	21 (50%)	28 (48%)	49
Fair "	16 (38%)	20 (35%)	36
Poor "	5 (12%)	10 (17%)	15

The results are almost the same in groups A and B. However, certain qualifications with reference to classification must be borne in mind. In certain patients the deliberate aim of treatment was a moderate reduction in pressure, and in these it would be unreasonable to claim only a fair or poor result where the blood-pressure reduction necessary to establish a good result had not been deliberately sought. Such limited results are looked for in patients who show evidence of severe atherosclerosis in cerebral or coronary arteries, or in patients with impaired renal function, in whom it is undesirable to produce a profound reduction in blood-pressure. It should also be noted that in the present series we have for the first time treated patients with relatively mild hypertension from a prophylactic standpoint. In this group with little or no evidence of hypertensive disease casual readings during relaxation are considerably lower. The aim of treatment is as much to "damp down" lability of the pressure as to lower resting pressures, and if this aim is achieved it is reasonable to claim a result as good. On the basis of the classification of Dollery and Harington (1962), in which a pressure of 160/100 or less in the standing position is stated to be good, the findings in 21 of our 42 severe cases and 38 of our 58 milder cases could be claimed as satisfactory.

Statistical analysis of the blood-pressure fall in the first 80 patients treated was carried out. Table IV shows the blood-pressure—mean and standard error of the mean. It also shows

the average fall in pressure, lying and standing, at the end of the period of observation, when the patient was on a stabilized regime. In some cases in which the pressure fluctuated considerably on consecutive visits to the clinic it was necessary to take average figures on the same dose.

TABLE IV.—Effect of Methyldopa on Blood-pressure in 80 Cases

	Position	Group A (Severe) (37)	Group B (Mild) (43)
Blood-pressure before treatment (mm. Hg)	Lying	{ S. 219.0 ± 3.60 D. 127.7 ± 1.30	201.9 ± 3.05 117.0 ± 1.38
	Standing	{ S. 208.8 ± 3.40 D. 130.5 ± 1.42	189.5 ± 2.43 118.0 ± 1.39
Blood-pressure fall on methyldopa (mm. Hg)	Lying	{ S. 40.1 ± 3.99* D. 21.3 ± 1.83*	30.3 ± 3.27* 16.2 ± 1.82*
	Standing	{ S. 56.0 ± 4.60* D. 30.8 ± 2.27*	42.0 ± 2.87* 20.1 ± 1.76*

S. = Systolic. D. = Diastolic. * $P < 0.001$.

Statistically the falls in pressure, both lying and standing, are highly significant, that in the lying position being approximately two-thirds that in the standing position. The decrease in pressure is rather greater in the more severe group, in which the initial pressures were higher. In both groups the end-result was about the same—namely, an average lying pressure of 175/105 and a standing pressure of 150/100.

Addition of Chlorthalidone

The addition of an oral diuretic was made for purely clinical reasons and not with a view to making any controlled observations. In 13 patients, however, chlorthalidone was added without making any other change in treatment or alteration in the dose of methyldopa, and in these patients a controlled comparison is therefore possible between the blood-pressure before and after the diuretic (Table V).

TABLE V.—Fall in Blood-pressure (13 Cases) After Addition of Oral Diuretic (Chlorthalidone 50 mg. Daily) to Stabilized Dose of Methyldopa

Position	Pressure	Fall in Blood-pressure (mm. Hg)	P
Lying	Systolic	26.9 ± 5.5	< 0.001
	Diastolic	13.5 ± 3.9	< 0.005
Standing	Systolic	31.2 ± 6.3	< 0.001
	Diastolic	13.9 ± 3.0	< 0.001

In four of these cases on ineffective doses of methyldopa the chlorthalidone made no difference. In the remaining nine it had a considerable effect in lowering the pressure, and, as shown in Table V, the effect was as great in the lying as in the standing position. It should be remembered, however, that the addition of chlorthalidone was often made for motives other than the mere reduction of blood-pressure, as already discussed under "drug regime."

Effect of Exercise

In 39 patients on long-term treatment standing blood-pressure were recorded after the patient had hurried up a flight of stairs. The results were variable and to some extent dependent on the degree of control over the blood-pressure which had been achieved. The maximum fall in pressure was 30/30 (systolic/diastolic) and the maximum rise 50/30. On the whole, those in whom the standing pressure was well controlled showed a fall on exercise (22 cases, average fall 7/8), while those with relatively high standing pressures, because the aim of treatment had not yet been achieved, generally showed a rise (17 cases, average rise 11/1). In no case did effort syncope occur. The exercise test is a good guide to whether the dose of methyldopa should be increased or not in doubtful cases.

Side-effects

Nearly three-quarters of the 100 patients experienced side-effects (Table VI), and it must be remembered that 14 additional patients observed during the same period stopped treatment because of side-effects. Drowsiness of a temporary nature experienced in the first week or two of treatment has been distinguished from persistent listlessness, which in some cases was present even after a year on methyldopa.

TABLE VI.—*Side-effects in 100 Cases*

	No. of Cases		No. of Cases
Temporary drowsiness ..	22	Diarrhoea ..	4
Persistent listlessness ..	19	Nightmares ..	4
Dryness of mouth and nasal congestion ..	16	Depression ..	4
Oedema ..	10	Muscular weakness ..	2
Dizziness (non-postural) ..	9	Impotence ..	2
Nausea ..	8	Miscellaneous* ..	4
Postural hypotension ..	7	Nil ..	28

* Includes one each of paraesthesiae, shivering attacks, malaise, and headaches.

Listlessness, malaise, and fatigue tended to be associated complaints and were more troublesome than with guanethidine. They cleared up if the drug was stopped, and consequently some patients had to abandon treatment with methyldopa. With rauwolfia compounds the complaint of malaise may include some impairment of intellectual functions, an effect which is naturally more evident in more intelligent patients. With methyldopa, malaise is more of the nature of a general feeling of being unwell. Dizziness in some cases seemed to occur without any relation to excessive lowering of blood-pressure. Depression occurred in six of our patients, and was the reason for stopping treatment in the early stages in one case. In another, suicide was attempted. In most cases, however, depression was mild in degree, and though there was no previous history of a similar complaint it was sometimes difficult to be sure whether this particular symptom was attributable to the drug or to the consequences of having hypertension, the necessity for treatment, and the knowledge that this would probably have to be continued permanently. Since depression has been reported by other authors, it must be accepted as a serious potential side-effect. Dreams or nightmares were another undoubted effect of methyldopa and have also been reported by other observers. In one case it was necessary to change the drug on this account and in another to decrease the dose. Nausea occurred in some cases and was occasionally associated with vomiting. Diarrhoea was usually mild and could be controlled by a small dose of a ganglion-blocking drug, codeine or propanthine: it rarely persisted after a few months.

It was notable that variations in severity of side-effects in different patients were not proportional to the degree of control over the blood-pressure.

Tolerance

By tolerance we mean that, initial control over the blood-pressure having been gained, a steady increase in the dose is required in order to maintain such control, if indeed it can be maintained at all. This occurred in only three of our cases, in marked contrast to the findings of some other workers. It is likely, however, that the differences between our results and those of others are differences in definition.

Intolerance

Twenty-five patients stopped taking the drug: of these, nine complained of symptoms similar to those experienced while off treatment or while taking other preparations. In some, the presence of another illness meant that there was a doubt about whether their symptoms were really attributable to methyldopa.

However, in 16 patients, six of whom had received methyldopa for less than six months, there appeared to be a specific intolerance to the drug. Most patients complained of several side-effects, the principal one, in each case leading to cessation of treatment, being drowsiness, listlessness in nine, diarrhoea in two, palpitation in two, and nausea, dizziness, and dryness of the mouth in one each. When side-effects were troublesome enough to necessitate stopping treatment this usually occurred early, often in the first three weeks. Once patients had got through this initial period treatment rarely had to be stopped.

Six patients died while taking methyldopa—five from uraemia and one from a subarachnoid haemorrhage. The last patient had reduced the dose of the drug two weeks prior to his haemorrhage because it was believed to be causing depression. In three uraemic patients methyldopa was used only in the terminal phase of their illness. In one other patient the drug had been discontinued, in view of disorientation, some time before she died of uraemia; but in the sixth case the onset of a rapidly fatal uraemic phase coincided with a change to methyldopa from another drug and may possibly have been precipitated by this change.

A variety of toxic effects of methyldopa have been reported. These included blood dyscrasias (Hallwright, 1961; Dollery and Harington, 1962; Hamilton and Kopelman, 1963), hyperpyrexia (Montegriffo, 1963), spontaneous lactation (Pettinger *et al.*, 1963), liver damage (Gillespie, 1960), skin rashes (Hamilton and Kopelman, 1963), and Parkinsonism (Grodén, 1963; Peaston, 1964).

We have not carried out repeated haematological or liver-function tests, nor have we routinely recorded the temperatures of our patients. Only one true case of toxicity was known to us in the series, and this occurred in a patient who developed an erythematous skin rash, which was correctly ascribed to methyldopa as a result of an on-off on-off trial.

Gain in Weight

All patients were weighed at each attendance, and after 12 months 64% showed a gain. The maximum gain was 16 lb. (7.3 kg.). The maximum loss was 13 lb. (5.9 kg.), and the average alteration was a gain of 2.28 lb. (1.03 kg.). From these particular calculations all patients who had received a diuretic were excluded. Also, in those patients to whom chlorthalidone was given, the weight immediately before the addition of the diuretic was compared with that achieved three months later. In this group, before starting diuretic therapy, an average gain of 3.5 lb. (1.6 kg.) had been recorded compared with the original weights, and after the addition of an oral diuretic an average fall of 2.1 lb. (1 kg.) was observed. It is therefore certain that a considerable part of the weight gained on methyldopa is due to fluid-retention. It might well be that if a full diuretic dose had been given the remainder of the increase would have been removed also.

Comparison of Methyldopa with Guanethidine

It was felt desirable to compare the relative effects of methyldopa with guanethidine so far as possible, since the latter drug was the one principally in use in this unit during the previous two years.

It was not practicable to carry out a double-blind controlled trial, and in order that the two groups should be comparable the comparison was made with only those patients with severe hypertension, as judged by the presence of grade 3–4 retinopathy and/or left ventricular hypertrophy on the electrocardiogram. Accordingly 37 patients under treatment with methyldopa were compared with 66 patients on guanethidine. Thiazide diuretics were used in roughly the same proportion of both groups and for the same reasons.

The results of treatment according to the standards applied by Lowther and Turner (1963) to guanethidine are shown in Table VII. It will be seen that the proportion of "good" and "fair" results achieved with methyl dopa is essentially the same as with guanethidine. The principal interest lies in the incidence of side-effects.

TABLE VII.—*Comparison of the Antihypertensive Effects of Methyl dopa and Guanethidine in Patients with Severe Hypertension*

Result	Guanethidine (66 Cases)		Methyl dopa (37 Cases)	
	No. of Cases	%	No. of Cases	%
Good	30	45	20	54
Fair	30	45	12	33
Poor	6	10	5	13

It is difficult to compare the precise incidence and severity of side-effects, because they are somewhat different in nature with the two drugs and are tolerated in varying degrees by individual patients. In general, postural symptoms, diarrhoea, frequency of micturition, muscular weakness, nasal stuffiness, and failure of ejaculation were more troublesome with guanethidine, while drowsiness, depression, fatigue, malaise, and dryness of the mouth were more common with methyl dopa. Fluid-retention and impotence may occur with either. More patients on methyl dopa, however, had no side-effects, and side-effects were milder and less persistent with this drug than with guanethidine.

The claim is sometimes made that methyl dopa differs from sympathetic blocking agents, such as guanethidine, in having a relatively greater effect on the supine blood-pressure. This hypothesis has been tested in two groups of comparable severity treated with methyl dopa and guanethidine. Table VIII shows the mean and standard error of the mean decreases in systolic and diastolic blood-pressures, supine and erect, for the two groups. There is clearly no difference between them ($P < 0.1$ in all comparisons) either in the magnitude of the blood-pressure fall or in the relative effects, lying and standing.

TABLE VIII.—*Fall in Blood-pressure on Treatment with Methyl dopa (37 Cases) Compared with Guanethidine (66 Cases)*

Posture	Pressure	B.P. Fall on Methyl dopa (mm. Hg)	B.P. Fall on Guanethidine (mm. Hg)
Supine ..	Systolic	40 ± 4.4	38 ± 4.8
	Diastolic	21 ± 2.3	26 ± 2.7
Erect ..	Systolic	53 ± 5.6	50 ± 5.0
	Diastolic	29 ± 3.0	31 ± 3.1

Discussion

A number of reports have been published in this country on the treatment of hypertension with methyl dopa, but mainly in relatively small series of patients treated for short periods.

Table IX summarizes the results of several previous papers and compares them with the findings of the present series. It will be seen that our results at the end of a longer period of following up and with a larger number of patients do not differ greatly so far as the overall results in terms of blood-pressure reduction are concerned. The difference between our own small incidence of tolerance and that of others has already been commented on. It is almost certainly a matter of differences in definition. Our results suggest that gain in weight is rather more extensive than other authors have reported, but comparisons can be made only where full information is given of the number of patients who had oral diuretics added to their drug regime.

The results of this trial show that methyl dopa is an effective long-term agent for lowering the blood-pressure in all grades of hypertension. Satisfactory control of the blood-pressure was obtained in about three-quarters of all cases, though to achieve this the addition of a thiazide diuretic was necessary in about

a third. A significant effect was produced on blood-pressure in the supine position, as with guanethidine; it amounted to some two-thirds of the decrease in standing blood-pressure. Side-effects occurred in about three-quarters of all cases.

TABLE IX.—*Side-effects. Summary of Published Series and of Our Results*

Reference	Irvine <i>et al.</i> (1962)	Baviss <i>et al.</i> (1962)	Dollery <i>et al.</i> (1962)	Doyle <i>et al.</i> (1962)	Daley <i>et al.</i> (1962)	Hamilton <i>et al.</i> (1963)	Smirk (1963)	Lauwers <i>et al.</i> (1963)	Present Series
No. of cases	15	20	59	40	20	65	19	17	100
Length of follow-up	< 6	2-12	1-10	1-14	1-16	1-14	< 9	1-14	6-36
Result:									
Good ..	13	19	32	26	16	46	16	14	49
Fair ..	2	1	10	14	2	14	3	3	36
Poor ..	0		17		2	5			15
Tolerance ..	0	7	Some	0	18	38	6	6	3
Side-effects:									
Drowsiness	11	20	Almost all	7	20	Most	34/44	11/28	41*
Depression	0	0	2	—	0	3	5/34	2/28	4
Dry mouth	15	2	3	7	6		23/34	8/28	
Nasal congestion	3	—	5	—	—	—	—	—	16
Indigestion	3	1	1	3	0	—	3/34	—	8
Diarrhoea	1	1	1	—	0	3	2/34	1/28	4
Weight gain	—	6	7	—	Some	26	—	—	64
Oedema ..	—	1	7	—	0	2	—	—	10
Impotence	—	—	1	—	—	—	—	2/28	2
Nightmares	7	—	—	—	—	—	3/34	—	4
Dizziness	—	—	—	—	—	—	—	—	16†

* Includes cases of persistent listlessness as well as temporary drowsiness.

† Both postural and non-postural cases.

In our experience the proportion of patients showing a good response as regards blood-pressure control is about the same as with guanethidine, pempidine, and mecamlamine. Advantages of methyl dopa, however, include the ease of adjustment in dosage, the absence of parasympathetic blockade, the less-disabling nature of the side-effects, the infrequency of serious toxic effects, freedom from syncope on effort, and the virtual absence of tolerance. We were also able to demonstrate that the relative decreases in supine and erect blood-pressure were the same with methyl dopa as they were in a series of patients treated with guanethidine, and this contradicts the claim frequently made that methyl dopa is more effective in controlling lying pressures.

Summary and Conclusions

One hundred patients have been treated with methyl dopa for periods of 6 to 36 months. The results have been analysed together with those of an initial double-blind trial in 11 patients and a group of patients who proved intolerant of the drug. Those with severe hypertensive disease were admitted to hospital for assessment and initial treatment. The remainder were assessed as out-patients, and all were subsequently followed in the hypertension clinic.

Details are given of the clinical features, method of assessment, and criteria for grading results.

Good control of the blood-pressure was achieved in 49%, fair control in 36%, and poor control in 15%. One-third of the patients were given chlorthalidone in addition to methyl dopa, and in 9 out of 13 of these, where comparison was possible, the oral diuretic had an effect in lowering the blood-pressure almost as great in the lying as in the standing position.

Side-effects were frequent, and occurred in 72% of patients. In general they were less disagreeable than those occurring with other drugs in recent use. The commonest were drowsiness, listlessness, dryness of the mouth, nasal congestion, and fluid retention.

In a comparison of two similar groups of patients treated with guanethidine and methyl dopa respectively the two drugs

appeared equally effective in controlling blood-pressure. In this series the fall of pressure in the supine position was no more pronounced with one drug than with the other. A higher proportion of patients were free from side-effects on methyl dopa than on guanethidine.

It is concluded that methyl dopa, though far from ideal, is as potent in reducing blood-pressure as previous drugs, and has the advantage of less frequent and less troublesome side-effects.

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REFERENCES

- Bayliss, R. I. S., and Harvey-Smith, E. A. (1962). *Lancet*, **1**, 763.
 Daley, D., and Evans, B. (1962). *Brit. med. J.*, **2**, 156.
 Dollery, C. T., and Harington, M. (1962). *Lancet*, **1**, 759.
 Doyle, A., and Trevaks, G. (1962). *Med. J. Aust.*, **2**, 55.
 Gillespie, L. (1960). *Ann. N.Y. Acad. Sci.*, **88**, 1011.
 Groden, B. M. (1963). *Brit. med. J.*, **1**, 1001.
 Hallwright, G. P. (1961). *N.Z. med. J.*, **60**, 567.
 Hamilton, M., and Kopelman, H. (1963). *Brit. med. J.*, **1**, 151.
 Irvine, R. O. H., O'Brien, K. P., and North, J. D. K. (1962). *Lancet*, **1**, 300.
 Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, **197**, 332.
 Lauwers, P., Verstraete, M., and Joossens, J. V. (1963). *Brit. med. J.*, **1**, 295.
 Lowther, C. P., and Turner, R. W. D. (1963). *Ibid.*, **2**, 776.
 Montegriffo, V. M. (1963). *Ibid.*, **2**, 35.
 Peaston, M. J. T. (1964). *Ibid.*, **2**, 168.
 Pettünger, W. A., Horwitz, D., and Sjoerdsma, A. (1963). *Ibid.*, **1**, 1460.
 Simonson, E. (1961). *Differentiation Between Normal and Abnormal in Electrocardiography*. Mosby, St. Louis.
 Smirk, Sir Horace (1963). *Brit. med. J.*, **1**, 146.

Transplacental Passage of Ampicillin

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Bacterial infection has been recently reported to account for 56% of deaths in England and Wales following abortion and for 5% of maternal deaths after the 28th week of pregnancy (Walker *et al.*, 1963). Butler and Bonham (1963) reported pulmonary infection as a primary necropsy finding in 13.3% of neonatal deaths in the first week of life, and considered that the majority of cases were of intrauterine origin.

There is some evidence available as to the value of antibiotics both in the treatment of maternal and foetal infections and in their prophylaxis. Smith *et al.* (1956), for example, found that combined therapy with streptomycin and oxytetracycline, given before delivery in cases of presumed intra-partum infection, reduced the perinatal mortality and the incidence of puerperal pyrexia. Leberherz *et al.* (1963), on the other hand, in a controlled trial involving 1,896 cases of premature rupture of the membranes found that demethylchlortetracycline, given by mouth after the membranes had ruptured, did not appear to reduce perinatal mortality due to infection, though the maternal morbidity rate was approximately half that in the control group. Anderson *et al.* (1962), studying congenital pneumonia, suggested certain absolute indications for antibiotic therapy during labour, and Theobald (1959) recommended that antibiotics should be given routinely after artificial rupture of the membranes, though neither he nor Anderson *et al.* give any further evidence to demonstrate the effectiveness of antibiotics used as they describe.

In reviewing the evidence, consideration must be given to the suggestion that factors other than bacterial invasion may produce inflammatory changes in the placenta, the membranes, and possibly also in the foetus (Bourne, 1962).

We decided to investigate whether ampicillin would cross the placenta to reach the amniotic fluid and foetal circulation in effective concentrations. Ampicillin has a wide spectrum of activity, is well absorbed after oral administration, and has a low incidence of side-effects in both adults and children

(Rolinson and Stevens, 1961; Brown and Acred, 1961; Knudsen *et al.*, 1961; Stewart *et al.*, 1961; Elliott *et al.*, 1964).

We have been able to find only one published report concerning the transplacental passage of ampicillin—namely, that of Elliott *et al.* (1964), who assayed ampicillin in amniotic fluid from four patients, and found only minimal concentrations.

Methods

The specimens tested included amniotic fluid and maternal sera obtained at the time of amniotomy or amniocentesis and maternal and foetal sera obtained at the time of delivery from many of the foregoing patients and from a small group of patients who were given ampicillin therapeutically during labour.

Ampicillin was given by mouth to 38 patients, in whom surgical induction of labour by low amniotomy was indicated on standard obstetric indications, in a dosage of 500 mg. six-hourly for five days. Specimens of amniotic fluid were obtained between three and one-quarter and five and three-quarter hours after the third dose of ampicillin. A mid-stream specimen of amniotic fluid was collected via a Currie catheter into a sterile container. In a further four patients, who had Rhesus antibodies, amniocentesis was performed in order to determine the bilirubin concentration in the amniotic fluid (Bevis, 1953; Walker, 1957). These four patients also were given 500 mg. of ampicillin six-hourly and amniocentesis was performed about four hours after the third dose. In all cases a specimen of maternal venous blood was taken at the same time as the specimen of amniotic fluid was collected.

At delivery, samples of cord blood and maternal blood were collected from the first group of patients and from three further patients who were given ampicillin in the same dosage for therapeutic reasons during labour. The number of doses of ampicillin given by the time delivery had taken place ranged from two to 13.

Amniotic fluid and sera were stored at 4° C. Specimens which could not be assayed within 24 hours of collection were

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