and increased in size in Case 7 despite further courses of methotrexate.

Summary

The rationale of methotrexate therapy is discussed and a short review of the literature given.

From January 1, 1960, to June 30, 1961, seven cases of chorionepithelioma were treated with methotrexate in the Gynaecological Department, University of Hong Kong. Summaries of the seven case records are given.

While hysterectomy, which was performed in all the seven cases, is thought to be necessary in the treatment of chorionepithelioma, the increase in size and number of pulmonary metastases in five of the seven cases seems to suggest that manipulation causes further spread of the disease. In the absence of profuse vaginal bleeding, therefore, methotrexate should be given before surgical extirpation of the uterus if a reasonably certain diagnosis is made. The optimal dose for a Chinese woman of average weight seems to be 100 mg. per course (5 mg. four times a day for five days). The dosage cannot, however, be calculated on the basis of body weight alone. The scheme used is described. The interval between courses is found to be two weeks in most instances. The number of courses should not be fixed, and methotrexate should be given until the male frog test becomes *persistently* negative, pulmonary opacities completely disappear, and secondaries elsewhere in the body completely resolve. While stomatitis is the commonest toxic manifestation of any significance, diarrhoea, generalized erythematous skin rash, and alopecia are also encountered.

Two patients (Cases 3 and 7) are dead, after having been treated with methotrexate for 6 and 10 months respectively. Two patients (Cases 1 and 5) have been lost trace of three months and one month respectively after the commencement of methotrexate therapy. Both of them were showing marked improvement when they were last seen. Three patients (Cases 2, 4, and 6) remain well with no sign of disease whatsoever 27, 22, and 12 months respectively after their first admissions.

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D

EFFECT OF METHYLDOPA IN CARCINOID DISEASE

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Alpha-methyldopa (alpha - methyl - 3,4 - dihydroxy - DL - phenylalanine) is an effective inhibitor of aromatic amino-acid decarboxylation in man (Oates *et al.*, 1960); as such it interferes with the synthesis of noradrenaline and serotonin.

Oates and his co-workers showed that the increased urinary excretion of 5-hydroxytryptamine (serotonin) that occurs after infusion of 5-hydroxytryptophan (5-H.T.P.) in normal subjects was greatly reduced during treatment with alpha-methyldopa. Two patients with the carcinoid syndrome were then given alpha-methyldopa (Sjoerdsma *et al.*, 1960). The excretion of the serotonin metabolite 5-hydroxyindoleacetic acid (5-H.I.A.A.) decreased by 60–70%, while there was a marked increase in the urinary excretion of 5-H.T.P. No significant effect on symptoms was apparent. Noble (1961) noticed subjective improvement in a man with the carcinoid syndrome who was treated with the L isomer of alpha-methyldopa, but there was no reduction in 5-H.I.A.A. excretion and 5-H.T.P. was not detected in the urine. Davis *et al.* (1961) gave alpha-methyldopa to four patients with the carcinoid syndrome with some relief from flushing in one patient but no symptomatic relief in the other three. In all cases 5-H.I.A.A. excretion was unchanged.

We have given the more potent L isomer of alpha-methyldopa (methyl dopa) to three patients with the carcinoid syndrome. In one there was marked clinical improvement with a decreased excretion of 5-H.I.A.A. in the urine; the second patient did not show any change; and the third could not tolerate methyldopa.

Case Histories

Case 1.—A 66-year-old man presented with a nine-months history of abdominal pain, loss of appetite, loss of weight, and frequent loose bowel motions. For six months he had noticed that his face was redder than usual and he had been told that he had a "drinker's nose." Over the same period he noticed flushing attacks two or three times a week. Although his face became flushed with the attacks he felt cold and was noted to have cool extremities. Severe abdominal pain occurred with each attack and was followed by diarrhoea. Wheezing was prominent with the attacks but also occurred in between.

On examination his face was flushed, there was evidence of loss of weight, and his liver, which was hard and nodular, was enlarged to four fingerbreadths below the costal margin. Blood pressure was 130/75 mm. Hg. An ejection systolic murmur which could be heard at the pulmonary area was loudest during a flushing attack. He later developed the signs of tricuspid incompetence. At laparotomy widespread metastases were found in the liver and throughout the peritoneal cavity. The histological appearances were those of carcinoid tumour. The excretion of 5-H.I.A.A. was 260 mg./24 hours.

Case 2.—A man aged 59 had a laparotomy after a history of three months' colicky central abdominal pain. A carcinoid tumour of the small bowel was removed, but there were several large metastatic deposits in the liver. Within two months he was having four loose bowel motions a day and developed attacks of flushing after taking alcohol. Blood-pressure was 200/105 mm. Hg and the fundi showed narrowing and tortuosity of the retinal arteries. A soft ejection systolic murmur was present, maximal at the apex but also heard down the left sternal edge. The 5-H.I.A.A. excretion was 78 mg./24 hours.

Case 3.—In 1950 a 58-year-old woman was admitted to hospital having had intermittent colicky abdominal pain for 18 months. A carcinoid tumour of the small bowel with peritoneal secondary deposits was found at laparotomy. In 1958 at a second laparotomy for rectal bleeding widespread secondary deposits were found in the peritoneum and liver. She had had flushing attacks about once a month and an occasional loose bowel motion, but was otherwise well. By December, 1961, she was having flushing attacks every two to three weeks and several loose bowel motions each day. Blood-pressure was 190/110 mm. Hg, but otherwise the cardiovascular system was normal. 5-H.I.A.A. excretion was 30 mg./24 hours.

Method

The patients remained on a constant diet while they were taking methyldopa; this diet contained between 700 and 800 mg. of tryptophan. The first two patients underwent a trial in which the dose of methyldopa was increased every third or fourth day to a maximum of 6 g./day, over three weeks. The third patient could not tolerate more than 1.5 g./day and had two periods of a fortnight on the drug. 5-H.I.A.A. excretion was estimated on 24-hour urine samples by the method of Udenfriend *et al.* (1955), and 5-H.T.P. excretion was assessed semi-quantitatively by the colour reaction with *p*-dimethyl aminobenzaldehyde applied to paper chromatographs of the urine (Jepson, 1955).

Results

Case 1.—Methyldopa caused a marked improvement in this man's symptoms. The facies were less florid, flushing attacks became fewer, his wheeze disappeared, and although the diarrhoea persisted the number of motions fell from 12 to 6 a day. A dose of 2 g./day had no effect on the 5-H.I.A.A. excretion in his urine, but as his dose increased there was a gradual fall from the initial level of 260 mg./day to a final level of 37 mg. when he was having 6 g. of methyldopa/day (see Chart). As the excretion of 5-H.I.A.A.

Effect of increasing dose of methyldopa on urinary excretion of 5-hydroxyindoleacetic acid (5-H.I.A.A.) in Case 1.

fell 5-H.T.P. appeared in the urine and gradually increased as the excretion of 5-H.I.A.A. fell further. His blood-pressure fell from 130/75 to 85/70 mm. Hg, both standing and lying, and although he felt dizzy when he walked he preferred this to his previous symptoms. When the trial finished he continued on 6 g. of methyldopa a day. The excretion of 5-H.I.A.A. remained between 35 and 50 mg./24 hours. Methyldopa was then reduced to 2 g./day and the 5-H.I.A.A. excretion rose to 70 mg./24 hours although he did not feel any worse. His blood-pressure was 90/70 mm. Hg. On two occasions he was given placebo tablets. Each time his 5-H.I.A.A. excretion rose to over 100 mg./24 hours and he felt worse. His flushed appearance became more marked, he felt miserable, and had increased diarrhoea. On one occasion his wheeze returned and flushing attacks were more frequent. His blood-pressure rose to 125/90 mm. Hg. On being given methyldopa his clinical condition improved on each occasion, so he has been maintained on 2 g./day.

Case 2.—During the trial period of three weeks this man did not notice a change in his symptoms; he continued to have four loose bowel motions a day and an occasional flushing attack. The 5-H.I.A.A. excretion did not change significantly from the initial level of 78 mg./24 hours and 5-H.T.P. did not appear in the urine. His blood-pressure fell from 200/105 to 130/80 mm. Hg.

Case 3.—Methyldopa caused more symptoms than the carcinoid tumour. The blood-pressure fell from 190/110 to 90/60 mm. Hg, and she had many hypotensive episodes. Severe nausea and abdominal pain developed which she attributed to methyldopa. There were no changes in either the frequency of the flushing attacks or the looseness of her bowel motions. 5-H.I.A.A. excretion was unchanged.

Discussion

The appearance of 5-H.T.P. in the urine of one of our patients is evidence that methyldopa can partially inhibit the decarboxylation of 5-H.T.P. to serotonin in man. As the excretion of 5-H.I.A.A. fell but did not return to normal values in the one patient inhibition is not complete; 5-H.I.A.A. excretion was unchanged in the other two patients. Sjoerdsma *et al.* (1960) found that in two patients 5-H.T.P. appeared in the urine during treatment with alpha-methyldopa while the urinary levels of 5-H.I.A.A. fell but did not reach normal values. 5-H.I.A.A. excretion was unchanged in five other patients given alpha-methyldopa (Davis *et al.*, 1961; Collini, 1961) and in two patients given methyldopa (Noble, 1961; Dubach and Blumberg, 1961).

The symptomatic improvement of our first patient with methyldopa was remarkable, as was his deterioration when he was switched to a placebo. Although diarrhoea decreased, wheeze disappeared, and flushing became less marked, it was the improvement in general well-being that was most noticeable. Flushing attacks in this man were accompanied by dyspnoea, abdominal pain, diarrhoea, and cold extremities. Flushing attacks of this kind, which are comparatively rare in patients with the carcinoid syndrome, have been shown to be accompanied by the release of serotonin (Peart and Robertson, 1961). The more common flush is a brighter red, hot, and without dyspnoea; there is evidence that these attacks depend upon release of a substance or substances other than serotonin (Peart and Robertson, 1961). Serotonin is responsible for intestinal motility (Bülbring and Lin, 1958), so that interference with serotonin synthesis would be expected to help diarrhoea in patients with the carcinoid syndrome.

Severe side-effects which include diarrhoea, more intense flushing, lethargy, somnolence, and hypothermia

were reported by Davis *et al.* (1961) in one patient treated with 4 g. of alpha-methyldopa. Similar side-effects were noticed by Collini (1961), who was able to give his patient only 1 g. of alpha-methyldopa for four days. Dubach and Blumberg (1961) had to stop treatment with 2 g. of methyldopa because their patient became disorientated and sluggish. Our third patient could not tolerate more than 1.5 g. of methyldopa because of hypotension and abdominal pain. Side-effects in hypertensive patients treated with methyldopa have been minor (Irvine *et al.*, 1962), so that it does seem that patients with the carcinoid syndrome are more sensitive to the drug. It is possible that in some patients small doses of alpha-methyldopa might actually stimulate serotonin production. Sourkes (1954) observed that alpha-methyldopa at low concentration stimulated dihydroxyphenylalanine decarboxylase. However, 5-H.I.A.A. excretion was not increased in the case with severe side-effects.

Methyldopa has been shown to lower blood-pressure in patients with moderate hypertension (Irvine *et al.*, 1962). Hypotension occurred in two of our patients with the carcinoid syndrome. In the first patient the blood-pressure fell in both standing and lying positions; in the other, hypotension was one of the reasons why she could not tolerate the drug.

The Table lists the reported cases of carcinoid disease treated with alpha-methyldopa or methyldopa, together with the effect of the drugs on symptoms and on urinary excretion of 5-H.I.A.A. and 5-H.T.P. Only 3 out of 12 had decreased excretion of 5-H.I.A.A., while three others showed symptomatic improvement without urinary

the third patient could not tolerate the drug because of hypotension, abdominal pain, and nausea.

Patients with the carcinoid syndrome who are troubled with diarrhoea or flushing attacks should have a trial of methyldopa.

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Preliminary Communications

Serum Enzymes in Carriers of Muscular Dystrophy

Recent reports (Chung *et al.*, 1960; Schapira *et al.*, 1960; Aebi *et al.*, 1962) have indicated that some clinically unaffected female carriers of muscular dystrophy of the Duchenne type show raised levels of aldolase and phosphocreatine kinase in their serum. Because it may thus be feasible to detect carriers in a reliable way these reports need to be confirmed as fully as possible. I therefore wish to report some preliminary findings in a survey of families of patients with this form of muscular dystrophy which in general support the findings of other workers.

CLASSIFICATION OF SUBJECTS

A similar classification to that of Leyburn *et al.* (1961) was used, and the subjects were divided into two groups:

1. *Known Carriers.*—These were mothers with two or more affected sons, or one affected son and a definitive history—for example, an affected brother or maternal uncle.

2. *Possible Carriers.*—These consisted of the following: mothers with only one affected son and no family history, female sibs and patients, maternal aunts of patients.

METHOD

Blood was collected in the normal way by venepuncture and allowed to clot for separation of the serum, which was then frozen at -25°C . In most cases estimations were carried out within a few days of collection, but when this was impracticable specimens were stored at -25°C . for not longer than two months.

Aldolase was estimated by the method of Friedman and Lapan (1958) and phosphocreatine kinase by the procedure of Hughes (1962).

Reported Cases of Carcinoid Disease Treated with Alpha-methyldopa or Methyldopa. Effect of the Drugs on Symptoms and Urinary Excretion of 5-H.I.A.A. and 5-H.T.P.

Author	Urinary 5-H.I.A.A. Excretion	Urinary 5-H.T.P. Excretion	Symptoms		
			Flushing	Diarrhoea	Others
Sjoerdsma <i>et al.</i> (1960)	↓	↑	—	—	—
Nicholson <i>et al.</i> (1962)	1 ↓	1 ↑	Improved	Improved	Improved
	2 Unchanged	2 Nil	Unchanged	Unchanged	Unchanged
	3 " "	3 " "	" "	" "	Abdominal pain
Noble (1961)	" "	" "	Improved	Improved	—
Collini (1961)	" "	" "	Worse	Worse	Worse
Davis <i>et al.</i> (1961)	1 " "	1 " "	Unchanged	Improved	" "
	2 " "	2 " "	" "	Unchanged	—
	3 " "	3 " "	" "	" "	—
Dubach and Blumberg (1961)	" "	" "	" "	Improved	Worse

changes. Sjoerdsma *et al.* (1960) do not report the symptomatic effect of alpha-methyldopa on their patients. The differing response is not explained. Failure to absorb methyldopa could have occurred in the patients who showed no change. It is unlikely that methyldopa will help many patients with the carcinoid syndrome, but in view of the success with our first case it should be given a trial, especially in patients with severe symptoms.

Summary

Methyldopa, a drug which interferes with the synthesis of serotonin, was given by mouth to three patients with the carcinoid syndrome. In one there was marked clinical improvement, with decreased excretion of 5-hydroxyindoleacetic acid in the urine and increased excretion of 5-hydroxytryptophan; the symptoms of the second patient were unchanged, while