and more rapid relief of pain than the lower dose range, as 18 out of 22 patients obtained relief within the first four hours, a matter of importance in such a painful condition. The decisive factor would seem to be the severity of the gouty arthritis.

Boardman and Hart (1965) reported no response to indomethacin in four females with gout, but the two females in the group under study responded in a manner quite indistinguishable from that of the males—again the difference in response may be one of dosage. It would seem that the higher the dosage used the more rapid the response and the greater the proportion of patients responding. The factors limiting dosage then become the cost and the incidence of side-effects.

Reports of the use of indomethacin in other joint diseases (Hart and Boardman, 1965 ; Smyth, 1965) have included a high incidence of headache, giddiness, nausea, or vomiting. The incidence seemed to depend largely upon the daily dose of indomethacin administered, ranging from 30 to 80% with daily doses of 100 to 200 mg. This trial has therefore been unusual for the low incidence of side-effects found. Boardman and Hart (1965), using doses which sometimes reached 600 mg. daily, found a 30% incidence of side-effects in their gouty patients ; they also commented that these were not severe. Their lower dosage was therefore not associated with any reduction in the incidence of side-effects, though they thought that side-effects were less severe in younger patients. It seems possible that patients with acute gout, who are relatively young and otherwise healthy, may be more tolerant of the side-effects of indomethacin than patients suffering from a chronic debilitating disease such as rheumatoid arthritis.

Summary

The results of treatment with a regimen of indomethacin therapy in 22 patients with acute gouty arthritis are described. The regimen consisted in administering 100 mg. of indomethacin by mouth four-hourly until most of the pain was relieved, after which administration was continued at eight-hourly intervals with three doses of 100 mg., three of 75 mg., and three of 50 mg. This method has been shown to be very effective in producing rapid relief of pain and subsidence of the acute gouty arthritis and to be associated with a low incidence of side-effects.

I wish to acknowledge the assistance of the nursing staff of the university wards at the Princess Alexandra Hospital and their care in attending to details of administration and recording the response to treatment. I am grateful to Merck, Sharp, and Dohme (Australia) Pty. Ltd. for generous supplies of indomethacin (Indocid).

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Vasodilator Properties of Alcohol

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The facial flushing associated with the consumption of alcohol is a well-recognized phenomenon, and alcohol, often in the form of whisky, has been widely recommended as a useful peripheral vasodilator agent. There have been very few quantitative measurements reported of its effects on peripheral blood-flow in normal subjects, however (Abramson *et al.*, 1941), and none in subjects with ischaemic legs, though intra-arterial alcohol therapy has been described (Edwards *et al.*, 1952 ; Conrad and Green, 1964). The present paper gives the results of measurements undertaken to establish quantitatively the nature of the vasodilatation produced by alcohol, with particular reference to the effect of whisky on blood-flow in the legs both of healthy subjects and of those with occlusive peripheral arterial disease. The results have been compared with those obtained with the more commonly used vasodilator drugs, and the possible practical usefulness of whisky as a vasodilator is assessed. Brief mention is made of some pharmacological aspects of the vasodilator action of alcohol.

Methods

Blood-flow in the feet, calves, forearms, and wrists of healthy adult subjects, and of patients with occlusive arterial disease affecting the legs, was measured by venous occlusion plethysmography by means of mercury in rubber-strain gauges (Whitney, 1949). Plethysmograms from the wrist and foot are a record mainly of skin blood-flow, while those from the forearm and calf indicate largely muscle blood-flow. Blood-flow in the upper limb was also measured in patients after cervicodorsal sympathectomy for Raymond's phenomenon and hyperhidrosis. In all subjects alcohol was given either orally, in the form of Scotch whisky in a dose varying from 1 to 3 ml./kg. of body weight, or as a brachial-artery infusion of ethyl alcohol from a motor-driven syringe.

In each experiment the subject, after a light meal, lay for approximately half an hour in the laboratory until his peripheral blood-flow was at a steady level. Thereafter the control resting blood-flows in the areas being investigated were recorded four times a minute for five minutes. When whisky was to be given orally it was taken, usually undiluted, during the next four minutes, and further blood-flows were measured for three- or four-minute periods at intervals of 15 minutes or less for the duration of the experiment. Venous blood was withdrawn for estimation of its alcohol content 30 and 60 minutes after consumption of the whisky, and at the end of the experiment the subject's urine was also collected for alcohol estimation. The alcohol content was measured by a modified Cavett method in the forensic laboratory of St. George's Hospital. In setting out the results of these experiments the blood-flow at any period has been expressed as the mean of all inflows recorded for that period, and, unless otherwise stated, all measurements in subjects given whisky orally relate to a dose of 2 ml./kg. of body weight.

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Results

A wide range of blood and urinary alcohol levels were measured in 26 subjects after they had drunk 2 ml. of whisky per kg. body weight, but in all of them a significantly high alcohol level was achieved during the period when blood-flow was measured (Table I); the blood alcohol level averaging 76 mg./100 ml. at half an hour and 92 mg./100 ml. at one hour.

TABLE I.—*Blood and Urine Alcohol Levels in 26 Subjects Given 2 ml. Whisky per kg. Body Weight*

	Whisky Given (ml.)	Blood Alcohol (mg./100 ml.)		Urine Alcohol at 60 min. (mg./100 ml.)
		At 30 min.	At 60 min.	
Range	80–180	17–149	46–224	27–92
Mean	125	76	92	59

Effect of Alcohol on Skin Blood-flow

The effect of such a blood alcohol concentration on resting blood-flow in the foot of a healthy subject is shown in Fig. 1; it will be seen that whisky does produce a large increase in peripheral blood-flow. The results of similar measurements in one foot of 12 healthy subjects are shown in Fig. 2. The resting pedal blood-flow is increased on an average some five and a half times at the end of one hour, by which time the vasodilatation has usually reached its maximum, and similar,

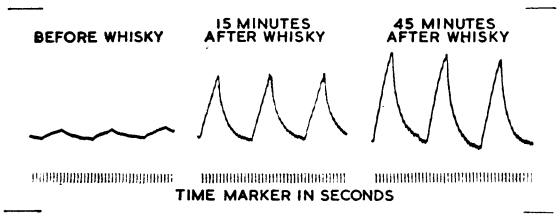

FIG. 1.—Plethysmogram illustrating the large vasodilatation produced by whisky in a healthy subject's foot. (Dose of whisky 2 ml./kg. body weight.)

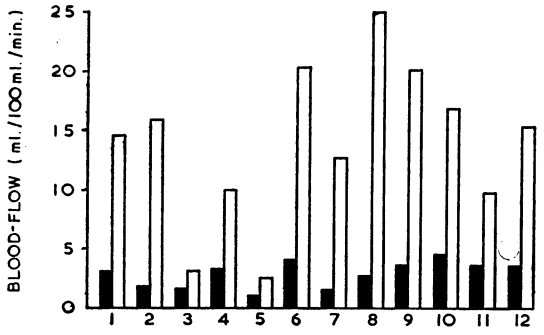

FIG. 2.—Foot blood-flow in one leg of 12 healthy subjects before (solid columns) and one hour after (open columns) whisky. (Dose of whisky 2 ml./kg. body weight.)

TABLE II.—*Effect of Whisky on Blood-flow at Left Wrist in Eight Healthy Subjects*

Subject No.	Blood-flow in ml./100 ml. tissue/min.				
	Before Whisky	Minutes After Whisky			
		15	30	45	60
1	15·3	—	—	—	65·3
2	3·1	9·2	20·0	21·5	31·0
3	3·4	34·6	37·7	41·9	46·2
4	9·1	24·0	33·8	53·6	49·0
5	8·4	14·9	20·0	19·3	19·8
6	21·9	43·8	48·0	40·8	—
7	16·6	45·0	33·4	40·3	43·2
8	3·5	29·3	26·8	26·5	5·8

There is a large increase in blood-flow persisting at one hour in all patients except No. 8. This patient was given whisky in a dose of only 1 ml./kg. body weight, while the others had 2 ml.

or even larger, increases of blood-flow at one wrist of eight healthy subjects were also measured (Table II). The vasodilatation after whisky is greater than that previously produced in 50 healthy limbs by various commonly used vasodilator drugs given intravenously (Gillespie, 1959). Great as it is, however, whisky vasodilatation is not a maximal one, for the pedal post-ischaemic hyperaemia which followed the release of an arterial tourniquet, inflated for three minutes in three subjects, resulted in a further brief doubling, at least, of blood-flow, even at the height of alcohol vasodilatation.

There is thus no doubt that whisky is a potent cutaneous vasodilator in normal subjects. It is necessary, however, to ascertain whether it still produces a good vasodilatation in limbs with arterial occlusions; a situation in which it is now widely accepted that the common peripheral vasodilator drugs are usually ineffective. In 11 limbs with blocked arteries, in seven patients, whisky did increase pedal blood-flow, on average three and a half times one hour after it was drunk (Fig. 3). While the increase in blood-flow produced in these limbs is only about half that produced in limbs with healthy arteries, it is still significant. It might thus appear that whisky could have a therapeutic value in the role of a vasodilator. However, none of these 11 feet, in spite of the arterial occlusions, showed evidence of ischaemia, nor was there rest pain, and such patients do not require a vasodilator, as their feet still have an adequate blood-flow.

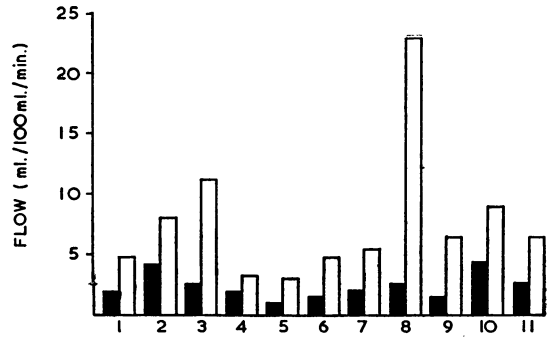

FIG. 3.—Foot blood-flow in 11 limbs with arterial occlusions, but healthy feet, before (solid columns) and one hour after (open columns) whisky. (Dose of whisky 2 ml./kg. body weight.)

The vasodilator effect of whisky, by contrast, was found to be poor when it was measured in six feet of patients with objective signs of ischaemia, often associated with mild rest pain but not gangrene (Fig. 4). In none of these limbs was there any large increase in blood-flow, and in two the flow was actually reduced—a well-recognized phenomenon in the feet of limbs with occluded arteries when generalized vasodilatation is produced. These results are disappointing, as it is only in these very patients that one might wish to use a vasodilator.

Finally, to determine the extent of vasodilatation produced by a smaller dose of whisky than 2 ml./kg. body weight, five subjects were given only 1 ml. Their blood alcohol level at one hour was usually less, and a smaller and shorter-lived increase in pedal blood-flow resulted, even when the arteries were healthy; in two subjects no significant residual vasodila-

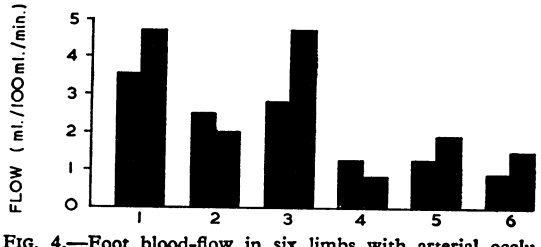

FIG. 4.—Foot blood-flow in six limbs with arterial occlusions and pedal ischaemic signs before and one hour after whisky. (Dose of whisky 2 ml./kg. body weight.)

tation was measurable at one hour. The fact that the amount of whisky usually required to give a good sustained vasodilatation in healthy subjects seems to be about 2 ml./kg. body weight would have raised an important practical consideration in the possible use of whisky as a peripheral vasodilator if it had proved to be more efficient in the ischaemic foot. This quantity of whisky would be a large one to consume as a repeated form of therapy, amounting, for example, to 5½ oz. (156 ml.) in a 180-lb. (81.6-kg.) subject. While some patients might have found this medication to be highly palatable, others would have regarded it as unacceptable, both for social and economic reasons, and any relief of pedal rest pain after such dosage could well be due to the cortical effects of alcohol, rather than to any peripheral vasodilator action.

Effect of Alcohol on Muscle Blood-flow

Whisky proved to have little or no effect on muscle blood-flow, the vasodilatation it produced being solely cutaneous. This is illustrated by its effects on the right wrist and left forearm flows, recorded simultaneously, in a healthy subject (Fig. 5). There is a good increase in blood-flow at the wrist, where the total flow is mainly in skin, but little change in the forearm, where the total flow is mainly in muscle. The results of similar measurements in the foot and calf of five healthy subjects are set out in Table III, and the different effect on skin and muscle blood-flow is confirmed.

FIG. 5.—Plethysmogram illustrating the lack of effect of whisky on forearm blood-flow (top trace) of a healthy subject, compared with the large vasodilatation produced in the foot (bottom trace). (Dose of whisky 2 ml./kg. body weight.)

TABLE III.—*Comparison of Effect of Oral Whisky on Foot and Calf Blood-flow, Recorded Simultaneously, in Five Healthy Subjects*

Subject No.	Blood-flow in ml./100 ml. tissue/min.			
	Right Foot		Left Calf	
	Before Whisky	1 hr. After Whisky	Before Whisky	1 hr. After Whisky
1	2·7	14·7	5·2	4·3
2	1·3	15·7	3·1	2·7
3	3·0	16·3	3·4	4·6
4	2·9	11·2	4·9	6·6
5	1·0	2·8	6·5	4·5

Foot blood-flow is greatly increased in all subjects except No. 5, who was given whisky in a dose of only 1·5 ml./kg. body weight. No. 4 was given 3 ml., and the remainder 2 ml./kg. body weight. Calf blood-flows are little changed.

In its lack of effect on the muscle circulation whisky resembles the vasodilator drugs in common use (Gillespie, 1963), though the mechanism of its action on skin vessels is almost certainly different, as shown below. Neither whisky nor other vasodilators have any place in the treatment of intermittent claudication.

Effect of Alcohol on Skin Blood-flow in Sympathectomized Limbs

Of special interest in regard to the mechanism of action of alcohol as a vasodilator was the observation that in eight sympathectomized upper limbs of six subjects oral whisky produced a marked increase in skin blood-flow, even when operation had been carried out only 24 hours previously (Table IV). Alcohol, therefore, unlike the vasodilators in common use, does not produce its vasodilator effect purely by peripheral sympathetic blockade or central inhibition.

TABLE IV.—*Effect of Whisky on Wrist Blood-flow in Eight Sympathectomized Limbs of Six Subjects Treated for Primary Raynaud's Phenomenon or Hyperhidrosis*

Limb	Time since Operation (days)	Blood-flow in ml./100 ml. tissue/min.				
		Before Whisky	Minutes After Whisky			
			15	30	45	60
1	1	27·1	29·7	33·7	44·2	35·7
2	1	15·2	20·4	22·8	25·9	19·6
3	3	17·5	25·2	31·6	26·8	39·8
4	3	4·0	6·0	7·6	6·9	7·4
5	4	16·9	18·2	29·4	26·1	29·4
6	6	25·3	38·9	39·1	38·9	42·6
7	72	20·6	23·5	27·2	32·9	28·4
8	240	2·2	4·1	3·7	3·4	3·7

It will be noted that flow is increased in all limbs, even in those sympathectomized only very recently. All subjects were given whisky in a dose of 2 ml./kg. body weight.

Effect in Intra-arterial Infusion of Alcohol

Varying concentrations of ethyl alcohol were infused into one brachial artery of three healthy subjects while blood-flow at the wrist and in the forearm was measured. The highest dose of alcohol given this way was a 10% solution infused at a rate of 3.75 ml. a minute, but there was no increase in either skin or muscle blood-flow compared with flow in the contralateral control limb; in fact both skin and muscle blood-flows were decreased. Mental arithmetic undertaken during the experiment, and substituting tolazoline for alcohol in the infusion, caused the expected immediate increase in skin blood-flow (Fig. 6).

It thus appears that alcohol acts as a vasodilator only when it has been partly metabolized, presumably in the liver, and it has a direct vasoconstrictor effect when it is infused intra-arterially. It was noted in the one healthy subject in whom it was investigated that an equivalent oral dose of ethyl alcohol produced almost the same cutaneous vasodilatation as had previously been produced by oral whisky, so that the vasodilator action of the latter is not due to the presence of its many other constituents apart from alcohol.

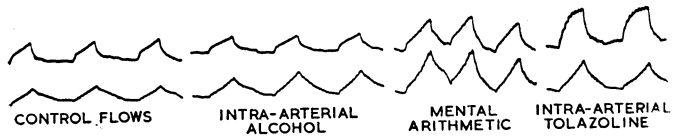

FIG. 6.—Plethysmogram comparing the blood-flows at the wrists of a healthy subject. Infusion of 10% alcohol at 3.75 ml./min. into the left brachial artery (upper trace) decreases skin flow. Doing mental arithmetic results in a good increase in both limbs, and there is a brisk vasodilatation at the left wrist in response to intra-arterial tolazoline.

Summary

Oral alcohol in the form of whisky has been shown by blood-flow measurements to be a good peripheral vasodilator in healthy limbs, being even more effective in this respect than the normal vasodilator drugs, though the dose required to produce sustained good vasodilatation in healthy subjects may be as much as 2 ml./kg. body weight. It has a good capacity for increasing pedal blood-flow in limbs with occluded arteries provided the feet themselves are healthy. When the feet are already ischaemic, vasodilatation is uncertain and small, however, and blood-flow may even be reduced. For these reasons whisky, considered purely as a vasodilator, would seem to have little place in the treatment of pedal ischaemia.

In recently sympathectomized upper limbs whisky produced significant increases in skin blood-flow; thus it does not produce its effects simply by peripheral sympathetic blockade or central inhibition.

Intra-arterial infusion of alcohol produced a decrease in skin blood-flow, so that the vasodilator effect of oral alcohol is not a direct one.

Alcohol decreases muscle blood-flow.

I wish to express my thanks to Mr. William Brough for much technical assistance; also to Mr. John Hynd. Mr. P. Hammond and Mr. V. Scoon kindly undertook the alcohol estimations.

Postscript.—Since this paper was submitted for publication J. D. Fewings, M. J. D. Hanna, J. A. Walsh, and R. F. Whelan (*Brit. J. Pharmacol.* 1966, **27**, 93) have recorded the results of a plethysmographic study of the effects of ethyl alcohol on the blood vessels of the hands and forearms of healthy subjects. Their observations are similar to those reported above for healthy upper limbs. However, they failed to detect any increase in blood-flow in the hand of one patient sympathectomized five years previously or in one patient with a brachial plexus avulsion, and thus inferred that alcohol vasodilatation was sympathetically mediated. In the present investigations all eight sympathectomized upper limbs showed vasodilatation —large in six of them—even shortly after operation, when the denervated hand was hot and flushed compared with the unoperated hand.

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Pyuria in Infancy, and the Role of Suprapubic Aspiration of Urine in Diagnosis of Infection of Urinary Tract

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The many studies of infections of the urinary tract in infants and children show how far we are from knowing the natural history of this disease. Even in the absence of structural abnormalities of the urinary tract infections appear to be common. It is clear that progressive renal damage can occur with so few symptoms that the presenting signs may be due to hypertension (Loyd Still and Cottom, 1967) or uraemia. It is suggested that many of these infections originate in the first year of life, and particularly in the first month (Stansfeld, 1966). Radiological abnormalities may be detected in up to 50% of infants and children presenting with infection of the urinary tract (Smellie *et al.*, 1964), and infection may be followed by scarring and impaired renal growth (Hodson and Wilson, 1965).

Positive diagnosis is fundamental to any study. It is unfortunate that most studies of urinary infection in infancy have rested upon the application of statistical probabilities to individual urinary findings. When, as with infants, a variable degree of specimen contamination is unavoidable, refinements in the techniques of cell and bacterial counting do not entirely eliminate diagnostic error. We feel that the uncertainties which surround the natural history of urinary infection in infancy will not be resolved until a method of obtaining uncontaminated infant urine is in general use. It was with this in mind that we applied to the study of the urine of newborn infants a method by which urine is aspirated from the bladder through the anterior abdominal wall. This technique, first described for infants by Pryles *et al.* (1959) and Pryles (1965), has already been used in adult surveys (Stamey *et al.*, 1965; Beard *et al.*, 1965), and in a study of premature infants by Nelson and Peters (1965). We here describe its application to a survey of urine findings in 162 healthy newborn infants. In a further small series we have assessed the value of suprapubic aspiration of urine in the diagnosis of infection of the urinary tract in infants and young children.

Patients and Methods

First Series.—Urine was collected from healthy neonates on about the sixth day. Only babies who were clinically well and were gaining weight satisfactorily were included. Clean specimens of urine were obtained with adhesive plastic bags,‡ by the technique normally employed in our neonatal nurseries. Instructions are given that the infant shall be carefully cleansed before the bag is applied, and that watch shall be kept so that specimens can be collected and refrigerated as soon as possible after micturition. Cell and bacterial counts were carried out by two of us (P. O'N. and A. P.) personally, using standard bacteriological techniques. Specimens were kept refrigerated and were cultured on the day of collection, except for three specimens which were refrigerated overnight. The technique of suprapubic aspiration is described in the Appendix.

Second Series.—This comprised infants and children seen in medical outpatient departments or in the wards. All had symptoms suggestive of infection of the urinary tract, but satisfactory urine specimens could not be obtained or had given ambiguous answers. Nineteen children have been investigated so far. Cultures, white cell counts, and colony counts were done by two of us (P. O'N. and A. P.), except in the case of a few specimens which were examined by clinical laboratory staff in the course of routine work.

Results in First Series

Clean-bag specimens were collected from 162 healthy newborn infants (99 male, 63 female).

Bacterial counts are shown in Fig. 1. The bacterial count exceeded 10^5 organisms/ml. in 104 of the 162 infants. Most cultures were mixed, but about one-quarter of all specimens yielded a pure or predominant growth of one type of organism only.

Cell counts are shown in Fig. 2. The sex difference is even more pronounced than that found by James (1959) and by Lincoln and Winberg (1964). In our series 90 of the 99 boys had white cell counts below 5/cu. mm., whereas 17 of the 63

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