TABLE IV

Executive Council Area	Mean Monthly Script Rate per 1,000 Population July-December, 1951 (and Standard Deviation)	Population Density per Acre	Average List Size
Banff*	301 (18)	0.14	1,614
Aberdeen	269 (35.2)	17.47	2,220
Glasgow	262 (33.6)	28.21	2,078
Fife	251 (20.7)	0.96	2,455
Dunbarton	242 (32.2)	1.06	2,520
Dumfries	241 (28.9)	0.13	2,180
Lanark	238 (27.8)	0.98	2,500
Stirling	230 (27.7)	0.70	2,370
Dundee	230 (32.4)	14.57	2,069
Ayr	230 (16.4)	0.45	2,255
Edinburgh	218 (28.4)	14.42	1,801
Angus	216 (18)	0.18	2,165
Aberdeen county	215 (9.8)	0.12	1,977
Renfrew	212 (27.7)	2.27	2,375
Roxburgh	206 (18.1)	0.10	1,769
Lothians	205 (17.9)	0.38	2,355
Argyll	188 (10)	0.04	1,240
Orkney	187 (16.1)	0.09	1,175
Perth	185 (14.6)	0.08	1,792
Ross	182 (12.9)	0.03	1,480
Galloway	182 (15.1)	0.07	1,742
Caithness	182 (9.3)	0.05	2,038
Sutherland	157 (8.3)	0.01	1,214
Inverness	151 (7)	0.03	1,484
Zetland	123 (10)	0.06	1,370

* See text.

The correlation between script rate and population density is an overall relationship, since associated with population density, though not necessarily dependent upon it, are such factors as the availability of the doctor, differential morbidity, the psychological attitude of the patient to disease, and the list size. Thus in urban areas the practitioner is usually conveniently available for a consultation and a prescription, often for very trivial maladies, in contrast to the Highlands and Islands of Scotland, where moor and fen, crag and torrent, and even stormy seas may intervene between the patient and doctor. Secondly, there may be an increased morbidity in the urban as opposed to the country population. Respiratory disease, as has been noted, is an obvious example. Thirdly, as Ferguson (1945) has suggested, the industrial population, perhaps because of family tradition, trade union example, habit, and economic pressure, are possibly more likely to declare themselves unfit for work than the rural population. To a bored, disinterested workman, with an unpleasant job in squalid surroundings and in the company of uncongenial associates, a very minor disability may perhaps be a welcome pretext to absent himself from work, and prescriptions follow.

Lastly, list size has been implicated as a cause for a high script rate, and this is suggested by Fig. 2. The overworked practitioner with an excessive number of visits to make and an inflated attendance at his surgeries may well find that it takes a long time to get a full history and to make a complete clinical examination, but only a short time to write a prescription. Nevertheless it will be readily understood that script rate may be related to list size simply because the latter depends upon population density. To assess accurately the significance of list size on script rate it would be necessary to obtain the figures for script rate in large as opposed to small practices among populations of similar density, but this information is not available. By an indirect approach, however, some evidence can be obtained to suggest that list size is not at any rate the sole factor involved, and probably not the most important one.

Table III shows a considerable monthly variation in the number of scripts issued in each area, and it is apparent that the degree of variation tends to be greater where the population is dense. There can be no doubt about the significance of the correlation shown by plotting the coefficient of variation against the population density (Fig. 3). This implies that the seasonal variation is relatively greater in densely populated areas. It is improbable that this can be entirely attributable to list size, and it is more likely to be due to other factors. If among these other factors the availability of the doctor and the psychological attitude of

the industrial worker towards disease are, as has been suggested, important, then the 1s. charge on prescriptions, which has been instituted since 1951, may be justifiable as a mild mass deterrent, though it is unfortunate that it penalizes the chronic sick without greatly discouraging the hypochondriac with a passion for medicine.

Summary

A survey has been made of 18,848 prescriptions on Form E.C.10 and of 1,569 E.C.10A forms issued in Scotland during the month of October, 1951, and the general pattern of prescribing has been analysed and reviewed.

In an attempt to elucidate the factors determining prescribing rates the number of scripts issued in the 25 executive council areas in Scotland in the months of July to December inclusive was contrasted with the population density and the average list size. A considerable degree of correlation was established, and the factors concerned are discussed.

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URINARY EXCRETION OF THE PRESSOR AMINES IN RELATION TO PHAEOCHROMOCYTOMA

BY

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The presence of adrenaline-like substances in human urine has acquired importance from the increase in the number of adrenal medullary tumours diagnosed during the past three years. Of cases of hypertension it appears that a certain percentage owe their symptoms to the release of adrenaline or, more usually, to the non-methylated substance *noradrenaline*, from an abnormal adrenal gland in which the medullary tissue is greatly hypertrophied. These patients suffer from intermittent attacks of high blood pressure, but there appear to be a few in whom the pressure is also raised above the normal between the attacks (Green, 1946). The diagnosis of the presence of such a tumour is a matter of importance, since its removal is followed by a disappearance of the symptoms.

Tumours examined (Holton, 1949; Swan, 1951) usually contain excessive amounts of active material. The normal suprarenal gland in man, obtained *post mortem*, was found by West, Shepherd, and Hunter (1951) in 36 cases to contain an average of 0.2 mg. of total pressor amine per gramme. This figure may be low, as in laboratory animals it is about 1 mg./g. Tumours have been found to contain from 2 to 20 mg. of total pressor amine per gramme, and this mostly *noradrenaline*. It is not surprising that the release of some active material causes a rise of blood pressure, and theoretically it should be possible to demonstrate active material in the blood. This is, however, not easy, and Engel and Euler (1950) showed that a large amount of *noradrenaline* can be found in urine.

Holtz, Credner, and Kroneberg (1947) were the first workers to show that human urine contained adrenaline, *noradrenaline*, and hydroxytyramine. This last substance

is relatively of low pressor activity. They found from 100 to 150 $\mu\text{g.}$ of adrenaline or *noradrenaline*, and 2 to 3 mg. of hydroxytyramine per 24 hours. They also stated, without giving figures, that urine from a subject with essential hypertension contained a larger amount of pressor substances than urine from a normal subject.

Euler and Hellner (1951) studied 24-hour urine specimens from 20 young normal subjects. They obtained mean values of 11 $\mu\text{g.}$ of adrenaline and 29 $\mu\text{g.}$ of *noradrenaline* per subject. They did not find sufficient hydroxytyramine in the extracts to interfere with the estimations.

In the present work the urinary output of pressor substances as obtained by Euler's method of extraction has been investigated. No attempt has been made to divide the pressor activity into adrenaline and *noradrenaline*; it has been estimated as though it were all *noradrenaline*.

Method

Extraction of Urine.—The urine was collected into a Winchester bottle containing 5 ml. of concentrated hydrochloric acid. It was stored in the refrigerator at about pH 3 whenever more than two days elapsed before it could be extracted. The volume was measured.

An aliquot of 300 ml. was adjusted to pH 1–2, and boiled under a reflux for 20 minutes. The acidity was checked during the boiling, as the solution tended to become alkaline. The hot urine was cooled in running water and 4 ml. of 20% (w/v) aluminium sulphate per 100 ml. was added. A smaller amount of aluminium sulphate solution very often failed to produce much precipitate, especially in concentrated urine. The cold urine was first neutralized with 20% (w/v) caustic soda, till the first appearance of aluminium hydroxide; and then the neutralization was completed with 2% caustic soda to pH 7.5, using phenol red as an external indicator. The solution was allowed to stand for 10 minutes, when the reaction was readjusted to pH 7.5.

The precipitate of aluminium hydroxide was separated by centrifuging at 800 g. for 5 to 10 minutes. The supernatant fluid was decanted off and the precipitate dissolved in 5N sulphuric acid. This solution was carefully neutralized with 20% caustic soda with vigorous mixing, till aluminium hydroxide just failed to be precipitated again; bromphenol blue, as an external indicator, became a greenish colour. This neutralization was important, because an acid solution depressed the blood pressure of the cat used for the final test.

A mixture of one volume of acetone and one volume of alcohol was then added and the solution allowed to stand in the refrigerator for one hour or more, usually overnight. The precipitate and crystals were filtered off and the filtrate was evaporated *in vacuo* to a small volume. This volume, together with the washings from the flask in which evaporation occurred, was 2–4 ml.

Biological Assay.—The extract was compared with a known solution of *noradrenaline* by intravenous injection into a cat anaesthetized with chloralose and given atropine to exclude vagal reflexes. The amount of the extract which caused the same rise of blood pressure as a given dose of *noradrenaline* was determined.

Results

Recovery of Added Noradrenaline.—To test the efficiency of the extraction process a specimen of urine was divided into two parts. To one part was added a quantity—for example, 100 $\mu\text{g.}$ —of *noradrenaline*. Both parts were then extracted, and the difference between the two assays gave the amount of *noradrenaline* recovered. In 20 observations the mean amount recovered was 100%, the values lying between 75 and 125%. As a further indication of the accuracy of the method, from one specimen of urine

two aliquots of 300 ml. were extracted, and both extracts were assayed three times. The figures obtained for the first extract were 29, 34, and 33 $\mu\text{g.}$, and those for the second extract 27, 29, and 29 $\mu\text{g.}$ Other pressor substances may be present in urine. These are piperidine (Euler, 1944), *isoamylamine* (Bain, 1914), tyramine (Bain, 1910), nicotine (Corcoran *et al.*, 1939), and the posterior pituitary hormone (Burn and Singh Grewal, 1951). A series of experiments was carried out in which each of these substances was added in large amount to a sample of urine. The urine was then extracted and tested. It was found that none of them appeared in the extract in sufficient quantity to be mistaken for *noradrenaline*.

Variation in Daily Excretion.—The excretion of *noradrenaline* was followed in one subject aged 31 for 14 successive days. The excretion per 24 hours varied from 16 to 86 $\mu\text{g.}$ on different days, which is about fivefold. The mean figure was 41 $\mu\text{g.}$

Influence of Age.—Urine from older people was found to contain a larger amount of *noradrenaline*. Table I contains the results on 38 subjects, divided into four age

TABLE I.—*Influence of Age on the Urinary Excretion of Pressor Amines Estimated as Noradrenaline. The Figures Were Obtained After Hydrolysis of the Urine*

Age Limits	Mean Age	No. of Subjects	Mean Noradrenaline ($\mu\text{g.}$)
3 months–10 years ..	6	9	18
23–30 years	27	12	59
31–40	32	10	64
41–63	50	7	71

groups. The mean excretion of children, aged from 3 months to 10 years, was 18 $\mu\text{g.}$ of *noradrenaline*. The mean excretion in the second group, young adults aged from 23 to 30, was 59 $\mu\text{g.}$ of *noradrenaline*. The difference between these two age groups is significant ($P=0.05$). The mean excretion in the two older groups aged 31–40 and 41–63 was 64 $\mu\text{g.}$ and 71 $\mu\text{g.}$ respectively. These figures are only slightly larger than the figure for the second group, but they conceal the wide variation observed. In adults of any age, the 24-hour excretion of *noradrenaline* may be at any value from 15 to 150 $\mu\text{g.}$

Free and Conjugated Noradrenaline.—Boiling the urine for 20 minutes at pH 1–2 hydrolysed any conjugated *noradrenaline* and rendered it free for adsorption on the aluminium hydroxide. If this preliminary hydrolysis was omitted some so-called “free” *noradrenaline* was extracted. The results in 12 adults and 9 children are shown in Table II.

TABLE II.—*Mean Excretion of Free and Conjugated Noradrenaline in $\mu\text{g.}$, by Night and by Day, for 12 Adults and for 9 Children. Night for adults was from bedtime to the time of rising. Day for adults was all the rest of the 24 hours. For the children, night was 6 p.m. to 6 a.m., the day 6 a.m. to 6 p.m.*

	Night			Day			Total		
	Free	Conj.	Total	Free	Conj.	Total	Free	Conj.	Total
12 adults	6	17	23	36	28	64	42	43	85
9 children	4	4	8	6	4	10	10	8	18

Conjugated *noradrenaline* was obtained by subtracting the figure for “free” from that for “total” *noradrenaline*, which was the result obtained after boiling the urine.

Essential Hypertension.—It is well known that older people commonly have a higher blood pressure than younger people, and one cause of this may be diminished destruction of pressor amines in the blood. Such a diminished destruction might result in increased excretion in the urine. The output of pressor amines was therefore determined in a series of subjects with a blood pressure less than 130 mm., and was compared with the output in a second series having

TABLE III.—*Relation of Excretion of Pressor Amines to Blood Pressure in the Middle-aged*

Normal Blood Pressures				Raised Blood Pressures			
Sex	Age	B.P. (mm. Hg)	Noradrenaline (μ g.)	Sex	Age	B.P. (mm. Hg)	Noradrenaline (μ g.)
M	52	95	90	M	55	135	150
M	50	115	85	F	50	140	70
F	45	120	60	M	59	155	120
M	48	120	150	F	35	170	67
M	45	120	83	F	57	180	94
M	46	122	69	F	63	190	61
F	63	130	22	F	57	200	36
				F	55	220	46
Mean	50	116	71		54	170	80

a blood pressure greater than 130 mm. The results are shown in Table III. The systolic blood pressures in the first group ranged from 95 to 130 mm., the mean being 116 mm.; those in the second group ranged from 135 to 220 mm., the mean being 170 mm. The ages in the two groups were similar, the means being 50 and 54 respectively. The mean output of pressor amines in the first group was 71 μ g. per day and in the second group 80 μ g. per day. Thus the subjects with the higher blood pressures did not excrete more pressor amine in the urine than the others.

Toxaemia of Pregnancy.—The excretion of noradrenaline was studied in cases of toxaemia of pregnancy associated with hypertension. The results are given in Table IV. A 24-hour collection of urine was made as soon as possible after the diagnosis, as rest in bed often caused the blood pressure to fall. The normal pregnancy group shown in the table were also resting in bed. Table IV shows that

TABLE IV.—*Relation of Excretion of Pressor Amines to Blood Pressure in Toxaemia of Pregnancy*

Normal Pregnancy			Toxaemia of Pregnancy		
Age	B.P. (mm. Hg)	Noradrenaline (μ g.)	Age	B.P. (mm. Hg)	Noradrenaline (μ g.)
28	100	26	31	130	38
34	100	57	32	130	46
31	100	63			
23	100	80	31	130	55
36	105	42	24	140	67
30	115	54	29	150	90
29	125	71	29	170	50
Mean: 30	106	56	29	142	58

there was no difference between the two groups, but the blood pressures of those with toxaemias were not very high.

Phaeochromocytoma.—In this series there were three cases of phaeochromocytoma, all suffering from paroxysmal hypertension. At operation an adrenal tumour was removed from each. Table V contains the figures for free and total noradrenaline. It is seen that the figures for noradrenaline are all greater than the highest normal figure, which is about 100 μ g. for free noradrenaline and 150 μ g. for total noradrenaline. In Case 2 of Table V the tumour itself was examined and found to contain 15 mg. of pressor amines per gramme, of which noradrenaline was about 50% and adrenaline 50%. In addition there were 10 cases of suspected phaeochromocytoma, some of whom were suffering from sustained hypertension and some from paroxysmal hypertension, and whose general symptoms and signs were consistent with the diagnosis. The output of noradrenaline

TABLE V.—*The 24-hour Output of Pressor Amines in Three Cases of Phaeochromocytoma*

Case	Sex	Age	Noradrenaline Output in 24 Hours (μ g.)	
			Free	Total
1	F	32	180	180
2	F	33	—	300
3	F	23	2,700	3,800

in these 10 cases ranged from 20 to 100 μ g., all being less than the highest normal figure of 150 μ g. No case has been operated on, but one patient died, and at the post-mortem examination the adrenal glands were found to be normal.

Discussion

The value of a determination of pressor amines in the urine seems to be confined to the diagnosis of phaeochromocytoma. Euler (1952) has stated that noradrenaline is excreted in increased amounts in a certain proportion of cases of hypertensive disease. Out of a total of 500 cases of hypertension he found that the excretion of pressor amines was normal in about 60% of the cases, but that it was increased in the remaining 40%. He has not yet published details to show the extent of the increase. It is difficult to compare this result with the present work, because the excretion of noradrenaline has been found to increase with advancing years.

The figures for the excretion in the three cases of phaeochromocytoma show a wide variation, and the lowest figure is not very much greater than the highest figure obtained for normal adults. It is reasonably certain that the excretion in patients who have these tumours will depend on the number of paroxysms which they suffer. On a quiet day with no paroxysms the excretion may be low. For certainty of diagnosis it is therefore important that the urine be examined for a period in which paroxysms have occurred.

Urine should not be collected on a day when a benzodioxane test has been carried out. In one case when this was done the benzodioxane test was negative, the systolic pressure rising from 200 to 260 mm. Hg, and the output of pressor amines in the 24-hour period was 490 μ g. An abnormally high output of pressor amines was not obtained in this case on three later days.

Green (1946) introduced a source of ambiguity when he showed that 37 out of 53 cases of phaeochromocytoma suffered from sustained hypertension. He defined sustained hypertension by the statement that the blood pressure did not fall between attacks to below 140 mm. systolic and 90 mm. diastolic, or that it did not fall below 95 mm. diastolic. He did not mean that the blood pressure was always at a constant high level.

On present evidence, however, the sustained hypertension of phaeochromocytoma should be marked by a high urinary excretion of pressor amines, while essential hypertension which is accompanied by paroxysms should not.

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