Possible role of catecholamines, corticosteroids, and potassium in production of electrocardiographic abnormalities associated with subarachnoid haemorrhage

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In a study of 40 patients with subarachnoid haemorrhage, of whom 24 were women of mean age 42 and 16 men of mean age 41, an attempt has been made to correlate electrocardiographic abnormalities with urinary normetanephrins and metanephrins, plasma cortisol, and with serum and total body potassium levels. Urinary normetanephrins and metanephrins, and plasma cortisol values were significantly raised in 19 patients with abnormal electrocardiograms compared with the 8 patients with normal cardiograms. In the former group urinary catecholamine and plasma cortisol concentrations remained at abnormally high levels throughout a 2-week observation period. Electrocardiographic features which showed a strong correlation with high urinary normetanephrin levels were a short PR interval and peaking of the T waves, and with high urinary metanephrin levels peaking of the P waves. Weaker, though significant, relations with high urinary catecholamines were shown by T wave inversion, long QTc, tall U waves, and Q waves. High plasma cortisol levels were significantly related to peaking of the P waves, a short PR interval, and peaking of the T waves. No significant differences in serum potassium levels in patients with either normal or abnormal electrocardiograms were revealed. Thirteen cases had total body exchangeable potassium measured about one week after subarachnoid haemorrhage, and abnormally low or low normal levels were observed in 9 of the 10 patients with abnormal or changing electrocardiograms. A second estimation of total body potassium in 6 cases, several months after the subarachnoid haemorrhage, showed higher values in 5 cases with one low normal remaining unchanged. No second estimation fell outside the normal range.

It was considered likely that the high urinary catecholamine and plasma cortisol levels arose from hypothalamic stimulation resulting from the haemorrhage. The possible mode of action of catecholamines upon the heart was discussed, with accent on the sensitizing effect of corticosteroids. This permissive role of corticosteroids probably stems from their ability to cause potassium deficiency, not reflected in serum levels, where a low myocardial intracellular potassium renders the heart susceptible to the necrotizing effect of catecholamines. It is, therefore, suggested that catecholamines, potentiated by corticosteroids and the associated potassium deficiency, are responsible for electrocardiographic abnormalities associated with subarachnoid haemorrhage, though a cause-and-effect relation has not been proved.

Electrocardiographic abnormalities occurring with subarachnoid haemorrhage were first described by Byer, Ashman, and Toth (1947). Their observations have since been confirmed by many studies (Hersch, 1964; Kreus, Kemilä, and Takala, 1969; Hunt, McRae, and Zapf, 1969) but the mechanism by

which the abnormalities are brought about has been a matter for speculation. Possible explanations have included hypokalaemia (Hersch, 1964), stimulation of area 13 under the frontal lobes (Cropp and Manning, 1960), hypertension (Kreus *et al.*, 1969), ischaemic heart disease (Sarner and Crawford, 1965), increased parasympathetic drive (Shuster, 1960), and increased sympathetic drive to the heart

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(Tomomatsu *et al.*, 1964). There is a good deal of indirect evidence to support this last suggestion (Lepeschkin *et al.*, 1960; Melville *et al.*, 1963; Reichenbach and Benditt, 1970; Sparks *et al.*, 1970; Hawkins and Clower, 1971; Hunt and Gore 1972). In contrast, direct evidence is scanty. Tomomatsu *et al.* (1964) and Eisalo, Peräsalo and Halonen (1972) estimated urinary catecholamines in a small number of patients with subarachnoid haemorrhage, and neither group demonstrated a correlation between electrocardiographic abnormalities and catecholamine levels. Russian workers (Iliynski and Astrakhantseva, 1967) showed a correlation in a minority of cases, but little detail was given. Though most studies have ruled out hypokalaemia as the cause (Wasserman *et al.*, 1956; Kung *et al.*, 1958; Finkelstein and Nigaglioni, 1961; Lichtlen and Schaub, 1962; Kreuz *et al.*, 1969), observations on total body exchangeable potassium have not been made. The integrity of the myocardial cell depends, among other things, upon the ratio of potassium concentrations inside and outside the cell membrane (Sodi-Pallares *et al.*, 1963). Thus changes in total body potassium, not necessarily reflected in serum potassium levels (Crooxon, Neutze, and John, 1972; Lockey *et al.*, 1966) have a pronounced effect upon the myocardial cell. Potassium deficiency, leading to low myocardial intracellular potassium, has been noted to sensitize the heart to the harmful necrotizing effects of catecholamines (Bajusz and Jasmin, 1964; Selye, 1970).

The present study was designated to investigate the relation between serially estimated urinary catecholamine levels and electrocardiographic abnormalities in subarachnoid haemorrhage. Adrenocortical activity was assessed, by measuring plasma cortisol levels, because corticosteroids are known to potentiate the effect of catecholamines upon the cardiovascular system (Raab, 1966; Selye, 1970). The interrelation between serum potassium levels, total body exchangeable potassium, and electrocardiographic abnormalities occurring in subarachnoid haemorrhage, was also studied.

Subjects and methods

The subarachnoid haemorrhage cases, proven by lumbar puncture, comprised 46 consecutive admissions to the Wessex Neurosurgical Centre. Six had a history of either hypertension or ischaemic heart disease and were omitted from the series. Of the remaining 40 cases, 16 were men with a mean age of 41 (range 13–56) and 24 women with a mean age of 42 (range 11–65). No patient was on diuretic therapy. All were taking a normal hospital diet.

On days 1, 2, and 3 after admission, and thereafter every 2 to 3 days over a 2-week period, the following investigations were done between 8.00 and 8.30 a.m.

- 1) A 12-lead electrocardiogram which was read by the

same person (J.M.C.) each time without knowledge of results of other investigations. Peaked P waves were defined as P waves taller than 2.5 mm; P mitrale as a bifid P wave wider than 0.10 sec; ST depression greater than 1 mm and elevation greater than 2.5 mm were regarded as abnormal; T wave peaking was defined as a T/R ratio in V₄ exceeding 0.6; the QTc was measured only when the U wave was visible, 0.43 sec being regarded as the upper limit of normal; 1 mm was regarded as the upper limit of normal for U wave magnitude. 2) A 24-hour urine collection was started for estimation of normetanephrins and metanephrins (breakdown products of noradrenaline and adrenaline, respectively) by the method of Stott and Robinson (1966). The upper limit of normal for both is 300 µg per 24 hours. 3) A venous blood sample was taken for (a) plasma cortisol estimation by the fluorimetric method of Mattingly (1962), the upper limit of normality being taken as 20 µg per 100 ml. (b) Serum potassium, the normal range being 3.5–5.0 mEq/l. 4) In 13 cases total body exchangeable potassium levels were estimated by an isotopic dilution method (Flear *et al.*, 1963): after 24 hours for equilibrium, the specific activity of 2 urine specimens passed within 1 hour of each other was measured. The error for the method is 5 per cent (Moore, 1963). Observed results were expressed in mEq and compared with the predicted result (± 2 SD) for age, sex, and weight of the patient, as read from regression lines based on age-grouped normal men and women (Moore, 1963). The ratio of observed total potassium to predicted total potassium (K_{obs}/K_{pred}), was a convenient means of expressing body potassium status. Total body potassium measurements were in most cases made about 1 week after the haemorrhage. In 6 cases with low levels a second estimation was made about 4 months later.

The 40 cases were divided into 3 groups: Cases with all normal electrocardiograms, cases with all abnormal electrocardiograms, and cases with changing electrocardiograms where some were normal and others abnormal. In the 8 cases with normal electrocardiograms, 6 were men of mean age 36 (range 13–54) and 2 were women of mean age 43 (range 42–44). The 19 cases in the abnormal electrocardiogram group comprised 5 men of mean age 48 (range 43–56) and 14 women of mean age 46 (range 16–65). The last group of 13 with changing electrocardiograms included 5 men of mean age 40 (range 16–54) and 8 women of mean age 35 (range 11–59).

Results

A total of 197 electrocardiograms was recorded, an average of 5 per patient. One hundred and fifty-two 24-hour urinary catecholamine and 89 plasma cortisol estimations were made. Types of electrocardiographic abnormality seen and their incidence are shown in Table 1, where numbers indicate cases who showed the particular abnormality on at least 2 occasions.

Mean urinary catecholamine and plasma cortisol levels in the electrocardiogram groups are shown in Table 2. Comparisons of the means were made by

TABLE 1 Types of electrocardiographic abnormality and their incidence in 40 cases

Type of abnormality	No. of cases	%
Tachycardia (> 100/min)	13	33
Bradycardia (< 60/min)	9	23
Extrasystoles	5	13
Wandering pacemaker	2	5
Peaked P waves	16	41
P mitrale	3	8
Short PR (< 0.13 sec)	10	25
Q waves	2	5
Raised ST segment	13	33
Depressed ST segment	3	8
Coved ST	6	16
Flat T	7	18
Inverted T	14	36
Peaked T	8	20
Tall U (> 0.1 mV)	13	33
Long QTc (> 0.43 sec)	22	55

the Student 't' test and the resulting P values are indicated in Table 3. The electrocardiographic features were analysed separately in an attempt to relate high urinary catecholamine and plasma cortisol levels to particular types of abnormality. Features having a significant relation with high urinary catecholamine levels are shown in Table 4. No statistically significant relation could be shown in the case of bradycardia, raised ST segments, coved ST segments, depressed ST segments, ventricular extrasystoles, or wandering pacemaker. The 3 components with a significant relation to high plasma cortisol levels are seen in Table 5.

Electrocardiographic components that were easily measured, namely the height of the P wave, PR interval, QTc, and height of U waves, were correlated with urinary catecholamine and plasma cortisol levels observed at the time of recording the electrocardiogram, and correlation coefficients (r) and P values are illustrated in Table 6. The QTc

TABLE 3 P values for comparisons of the mean values of normetanephrin, metanephrin, total catecholamines, and plasma cortisol levels in the 3 electrocardiographic groups (Table 2)

Electrocardiographic groups	Normetanephrin	Metanephrin	Total catecholamines	Plasma cortisol
Normal against abnormal	P < 0.01	P < 0.001	P < 0.001	P < 0.001
Normal against changing	N.S.	P < 0.05	P < 0.05	P < 0.01
Changing against abnormal	P < 0.01	P < 0.01	P < 0.01	N.S.

and U wave height showed no significant correlation with urinary catecholamine and plasma cortisol levels.

The relation between the time of the observations from the day of the subarachnoid haemorrhage on the one hand and urinary catecholamine and plasma cortisol levels on the other is shown in Fig. 1. It is apparent that in the normal electrocardiogram group, though the numbers of observations are relatively small, catecholamine and cortisol levels were within, or marginally above, the normal range throughout the whole period of 2 weeks or more. In contrast, in the abnormal group catecholamine and cortisol levels remained at abnormally high levels over the same period.

Mean serum potassium levels in the 3 electrocardiographic groups are shown in Table 7. There is no significant difference between the levels in the 3 groups and all are in the normal range. The total body potassium was normal in the normal electrocardiogram group but, with one exception

TABLE 2 Relation between electrocardiogram and 24-hour urinary normetanephrin, metanephrin, total catecholamines, and plasma cortisol.

Electrocardiogram	Mean urinary normetanephrin ($\mu\text{g}/24 \text{ hr}$)	Mean urinary metanephrin ($\mu\text{g}/24 \text{ hr}$)	Mean urinary total catecholamines ($\mu\text{g}/24 \text{ hr}$)	Mean plasma cortisol ($\mu\text{g}/100 \text{ ml}$)
All normal	267 (± 153) n = 23	218 (± 125) n = 23	485 (± 192) n = 23	15.0 (± 6.33) n = 16
Changing	320 (± 143) n = 52	290 (± 127) n = 52	610 (± 232) n = 52	22.9 (± 9.41) n = 30
All abnormal	479 (± 282) n = 77	376 (± 158) n = 77	855 (± 357) n = 77	25.8 (± 9.41) n = 48

n = number of observations.
Standard deviation is expressed as $\pm$.

TABLE 4 *Relation between mean 24-hour urinary normetanephrin, and total catecholamine levels (μg) and the various electrocardiographic abnormalities.*

<i>Electrocardiographic abnormality</i>	<i>Normetanephrin</i>	<i>Metanephrin</i>	<i>Total</i>
Tachycardia n=63	453 (± 260)	358 (± 151)	811 (± 376)
No tachycardia n=89	347 (± 188)	301 (± 137)	648 (± 278)
P value	<0.01	<0.05	<0.01
Peaked P wave n=65	452 (± 263)	366 (± 134)	818 (± 359)
Non-peaked P wave n=87	347 (± 187)	292 (± 146)	639 (± 291)
P value	<0.01	<0.01	<0.01
PR < 0.13 sec n=60	428 (± 260)	321 (± 112)	749 (± 350)
PR > 0.17 sec n=21	252 (± 109)	246 (± 103)	498 (± 165)
P value	<0.01	<0.05	<0.01
Peaked T n=30	528 (± 307)	384 (± 179)	912 (± 444)
Non-peaked T n=122	360 (± 190)	310 (± 132)	670 (± 280)
P value	<0.001	<0.05	<0.01
Inverted T n=80	431 (± 244)	348 (± 163)	779 (± 363)
Non-inverted T n=72	352 (± 198)	297 (± 116)	649 (± 283)
P value	<0.05	<0.05	<0.05
QTc > 0.43 sec n=51	441 (± 255)	361 (± 147)	802 (± 360)
QTc < 0.42 sec n=101	369 (± 208)	307 (± 140)	676 (± 308)
P value	N.S.	<0.05	<0.05
U wave > 0.1 mV n=62	428 (± 242)	343 (± 159)	771 (± 382)
U wave < 0.1 mV n=90	368 (± 211)	312 (± 133)	680 (± 288)
P value	N.S.	N.S.	<0.05
Q waves n=8	566 (± 444)	472 (± 258)	1038 (± 683)
No Q waves n=144	395 (± 228)	325 (± 149)	720 (± 334)
P value	<0.05	<0.05	<0.05

n = number of observations.
Standard deviation is shown as $\pm$.

(Case 11), was abnormally low or low normal in the changing and abnormal electrocardiogram groups (Fig. 2 and Table 8). Serum potassium levels do not appear to reflect total body potassium (Table 8). Of the 9 cases with abnormally low or low normal body potassium estimations, 6 had repeat measurements several months later (mean of 5 months, range 3 to 10 months). In 5 of these 6 cases, 3 with abnormally low and 2 with low normal levels, total body potassium levels had increased so that now all fell within the normal range for the particular weight (Fig. 2 and Table 8); the sixth patient (Case 8) showed a slightly decreased level but the difference was within the 5 per cent error for the method. All 6 cases had normal electrocardiograms at follow-up. When the estimations of total body potassium made within days of the subarachnoid haemorrhage are compared with those made months after the haemorrhage, the difference is statistically significant.

Discussion

Interpretation of the significance of 24-hour urinary catecholamine levels should be cautious. While urinary levels to some extent represent an overall estimate of sympathetic activity they are unlikely to reflect the influence of transitory changes. They are also dependent upon renal blood flow and function (Fluck, 1972). On balance, 24-hour urinary levels are possibly preferable to plasma levels which reflect the result of biosynthesis, catabolism, uptake, and release at the time of sampling, and may vary rapidly making interpretation of the significance of plasma catecholamine plasma levels difficult.

The three electrocardiographic groups were not homogeneous. The normal group contained a relatively small number of cases, with a preponderance of men; and the reverse was true for the abnormal and changing groups. A possible contribution of ischaemic heart disease to the electrocardiographic abnormalities could not be ruled out as there was a greater number of older patients in the abnormal

TABLE 5 *Relation between plasma cortisol and electrocardiographic abnormalities*

<i>Electrocardiographic abnormality</i>	<i>Peaked P wave n = 40</i>	<i>Non-peaked P wave n = 49</i>	<i>PR < 0.13 sec n = 11</i>	<i>PR > 0.17 sec n = 21</i>	<i>Peaked T wave n = 21</i>	<i>Non-peaked T wave n = 68</i>
Plasma cortisol ($\mu\text{g}/100\text{ ml}$)	27.0 (± 10.8)	20.7 (± 8.9)	27.5 (± 10.0)	18.9 (± 7.5)	27.3 (± 7.8)	21.9 (± 10.1)
P value	P < 0.01		P < 0.01		P < 0.05	

n = number of observations.
Standard deviation shown as $\pm$.

FIG. 1 Mean urinary normetanephrens (NMN), metanephrens (MN) in $\mu\text{g}/24$ hours, and plasma cortisol ($\mu\text{g}/100$ ml) levels in relation to time after S.A.H., a) in group with all normal electrocardiograms; and b) in group with all abnormal electrocardiograms. The number of observations is shown.

TABLE 6 Correlation between height of P wave and length of PR interval, and normetanephrin, metanephrin, total catecholamine, and plasma cortisol level

Electrocardio-graphic component	Normetanephrin <i>n</i> = 152	Metanephrin <i>n</i> = 152	Total catecholamines <i>n</i> = 152	Plasma cortisol <i>n</i> = 89
Height of P wave	<i>r</i> = 0.16	<i>r</i> = 0.30	<i>r</i> = 0.25	<i>r</i> = 0.27
P value	<i>P</i> < 0.05	<i>P</i> < 0.001	<i>P</i> > 0.01	<i>P</i> < 0.01
PR interval	<i>r</i> = -0.18	<i>r</i> = -0.11	<i>r</i> = -0.17	<i>r</i> = -0.16
P value	<i>P</i> < 0.05	<i>P</i> < 0.01	<i>P</i> < 0.05	N.S.

r = correlation coefficient.
n = number of observations.

TABLE 7 Serum potassium levels in the 3 electrocardiographic groups

Potassium levels		Normal electrocardiograms (8 cases)	Changing electrocardiograms (13 cases)	Abnormal electrocardiograms (19 cases)
Serum K level (mEq/l.)	n mean	22 3.8 (± 0.98)	62 3.7 (± 0.54)	96 3.6 (± 0.47)

n = number of observations.
Standard error of mean shown as $\pm$.

group. Differing electrocardiographic patterns of the three groups could not be accounted for by the timing of the sampling from the date of the haemorrhage, as the three groups were similar in this respect.

The variety and incidence of electrocardiographic abnormalities in the present study are similar to those in other studies. The high concentration of deaths and very ill patients in the abnormal group suggests that electrocardiographic abnormalities may have some prognostic significance, and this aspect, particularly in relation to cerebral artery spasm, is discussed elsewhere (Neil-Dwyer, Cruickshank, and Bira, 1974, in press). The findings of the present investigation do not support those of Galloon *et al.* (1972) which indicated that cases with a changing electrocardiographic pattern were

FIG. 2 Relation between electrocardiographic abnormality and total body exchangeable potassium approximately 1 week after haemorrhage and in 6 cases at follow-up several months later.

at high risk. Clearly a case for catecholamines being responsible for the electrocardiographic abnormalities in subarachnoid haemorrhage can be made, though a cause and effect relation is not proven. Abnormally high catecholamine levels over the whole 2-week period in the abnormal group (Fig. 1),

TABLE 8 Relation between electrocardiographic abnormalities and total body potassium approximately 1 week after subarachnoid haemorrhage and at follow-up several months later

Electrocardiogram type	Normal electrocardiograms			Changing electrocardiograms				
Case (sex and age)	1 M 13 yr	2 F 42 yr	3 M 54 yr	4 F 59 yr	5 F 18 yr	6 F 20 yr	7 M 54 yr	8 F 45 yr
Mean serum K (mEq/l.)	4.3	3.6	3.6	3.6	4.2	3.6	3.7	3.8
Total body potassium (mEq) 1 week after subarachnoid haemorrhage	Observed	2387	3209	3359	1977	1736	1418	2015
	Predicted	2480 (± 797)	2437 (± 541)	3172 (± 646)	2192 (± 541)	2083 (± 473)	2200 (± 473)	2950 (± 646)
Total body potassium (mEq) several months after subarachnoid haemorrhage	K obs/K pred	0.96	1.32	1.06	0.90	0.83	0.64	0.68
	Observed					1987	1906	2344
	Predicted					2083	2200	2950
	K obs/K pred					0.91	0.84	0.76
								0.77

Two standard deviations from predicted level shown as $\pm$.
The ratio of observed against predicted total body K = K obs/K pred.

so unlike the normal stress response (Moore, 1959), support this view. Electrocardiographic features showing a particularly strong relation with urinary normetanephrin levels were peaked T waves and a short PR interval, and with high urinary metanephrin levels peaked P waves. This latter observation supports the finding of Lepeschkin *et al.* (1960) that intravenous adrenaline caused peaking of the P waves. The relation between normetanephrin and the PR interval is in accord with observations on His bundle recordings (Damato *et al.*, 1969) which showed that catecholamines caused a pronounced shortening of the PH component of the PR interval. The peaked T wave - normetanephrin relation is consistent with the finding of Sparks *et al.* (1970) that T wave peaking resulted from injection of noradrenaline into the coronary artery of the dog. Electrocardiographic abnormalities showing a weaker relation with high urinary catecholamine levels were T wave inversion, long QTc, tall U waves, and Q waves. These changes have been shown to occur in response to catecholamine administration (Hecht and Anderson, 1947; Lepeschkin *et al.*, 1960; Haft *et al.*, 1972). In attempting to correlate these electrocardiographic abnormalities with high urinary catecholamine levels, certain sources of possible error were considered. Firstly, as already mentioned, difficulty exists in interpreting the significance of urinary catecholamine levels. Secondly, the type of catecholamine is important. Sparks *et al.* (1970) demonstrated 3 classes of

catecholamine with differing actions upon the electrocardiogram. For example, adrenaline and noradrenaline caused T wave peaking, while normetanephrins and metanephrins gave rise to T wave inversion. Complicated interactions of the three classes also occur. Thirdly, there is a pronounced individual variation in electrocardiographic response to any one type of catecholamine (Lepeschkin *et al.*, 1960).

The maintained high urinary catecholamine concentration in the abnormal electrocardiogram group was accompanied by plasma cortisol levels which remained abnormally high throughout the 2-week period. These results differ from those of Eisalo *et al.* (1972) who observed a fall in plasma cortisol levels after the first few days. The high cortisol levels showed a statistically significant relation with only 3 electrocardiographic features: positive in the case of peaked P waves and peaked T waves, and negative for the PR interval. With regard to the latter relation, it is of interest to reflect on the rationale for giving steroids to cases of complete heart block (Stock, 1969); Lown *et al.* (1955) noted a long interval in Addison's disease, while Cushing's syndrome was associated with a short PR interval which appeared to correlate with urinary steroid levels. The appropriate treatment for these diseases resulted in a return of the PR interval to normal. Jenkins *et al.* (1969) demonstrated pituitary-adrenal dysfunction in subarachnoid haemorrhage, with high nocturnal plasma cortisol levels. In the present study nocturnal plasma cortisol levels were not measured.

Plasma potassium concentration is sometimes taken to indicate the body's potassium status. The body potassium is, however, located mainly within the cells, less than 3 per cent being in the extracellular fluid. Hence potassium status is only indirectly reflected by plasma potassium levels. In fact Croxson *et al.* (1972), Lockey *et al.* (1966), and many others have found no useful correlation between plasma and total body potassium; and this has been confirmed in this investigation. Comparing serial readings of total exchangeable body potassium related to total body weight is a valid process provided body weight does not alter significantly during the period of observation. This was the case in the present study. Hypokalaemia did not appear to be a factor in the production of electrocardiographic abnormalities in this study. In contrast, total body potassium estimated about one week after the haemorrhage was, with one exception, low in the changing and abnormal electrocardiogram groups. A second total body potassium estimation several months later, in 6 of the 9 with low total levels, showed that the deficit had been wholly or

TABLE 8 (Cont'd)

Abnormal electrocardiograms				
9 F	10 M	11 F	12 M	13 M
35 yr	43 yr	53 yr	43 yr	56 yr
3.5	2.9	3.2	3.8	3.8
1950	2409	2274	2575	2677
2225	2967	2140	3132	3660
(± 541)	(± 646)	(± 541)	(± 646)	(± 646)
0.88	0.81	1.07	0.82	0.73
2783				3108
2225				3660
1.23				0.85

partially corrected in all but one patient in whom this remained unchanged.

Why potassium deficiency should have occurred in the first place is not immediately clear. No patient was on diuretic therapy and all had normal diets. Possible explanations are as follows: 1) potassium deficiency was, for some reason, present before admission to hospital; 2) enforced bed rest caused muscle wasting, but this would have affected all cases in similar fashion; 3) high plasma corticosteroid levels associated with changing and abnormal electrocardiogram groups caused intracellular and renal potassium loss; and 4) protein catabolism associated with stress (not corticosteroid dependent) leads to renal potassium loss (Allison, 1972). Though the first explanation cannot definitely be ruled out, the last two modes of potassium loss seem the most likely explanation for the low total body potassium observed in this study.

The mode of action of catecholamines upon the heart is not fully understood. Both transient and more permanent effects can occur. Transient effects stem from the property of catecholamines to modify cardiac electrical activity (Hoffman and Singer, 1967), in particular phases 2 and 3 of the monophasic action potential (Sparks *et al.*, 1970), where an increase in the slope of phase 3 causes T wave peaking and a decrease in the slope T wave inversion. T wave peaking sites (beta-receptors) and T-wave inverting sites (not alpha-receptors) exist (Sparks *et al.*, 1970), and the possibility of adenyl cyclase (which stimulates cyclic AMP) being the beta-receptor was discussed by Sutherland, Robison, and Butcher (1968). The more permanent effects occur when the physiological action of catecholamines, if carried to excess, produce pathological changes. Cardiac myofibrillar degeneration, frequently focal and subendocardial, has been well described (Reichenbach and Benditt, 1970) in association with pheochromocytomas or catecholamine administration. These authors also describe identical lesions occurring in the hearts of patients who died from subarachnoid haemorrhage. The ability of corticosteroids to sensitize the heart to the cardiotoxic effects of catecholamines (Raab, 1966; Selye, 1970) is probably an important factor in the production of electrocardiographic abnormalities in subarachnoid haemorrhage. This sensitizing action is almost certainly the result of potassium loss from the heart muscle, as a decrease in myocardial intracellular potassium content has been found to increase susceptibility to myofibrillar degeneration (Prioreschi, 1963; Bajusz and Jasmin, 1964). Other possible contributing factors to the cellular necrosis are relative anoxia resulting from increased oxygen requirements, and the ability

of catecholamines to aggregate platelets, leading to thrombus formation and cellular death (Haft *et al.*, 1972).

It is suggested that the mechanism of production of transient and more permanent electrocardiographic abnormalities in subarachnoid haemorrhage is as follows. The haemorrhage, by causing local cerebral arteriolar spasm, gives rise to ischaemic lesions in the hypothalamus and surrounding area (Crompton, 1963; Smith, 1963). This causes sympathetic stimulation of the heart, directly via the cardiac nerves and indirectly via the adrenal medulla. Stimulation of the hypothalamus has been shown to give rise to electrocardiographic abnormalities and to myocardial lesions resembling those seen in subarachnoid haemorrhage (Greenhoot and Reichenbach, 1969; Melville *et al.*, 1963). Such changes may be abolished by interruption of the sympathetic pathways in the high cervical region. Adrenalectomy, beta-blockade, or reserpine administration can prevent the development of electrocardiographic abnormalities and the myocardial lesions associated with simulated subarachnoid haemorrhage in animals (Burch *et al.*, 1967; Connor, 1969; Offerhaus and van Gool, 1969; Hawkins and Clower, 1971; Hunt and Gore, 1972). Hypothalamic stimulation, through the pituitary adrenocortical axis, has an additional effect upon the heart; it results in increased corticosteroid production which in turn depletes myocardial intracellular potassium, thus potentiating the cardioneurotic effects of catecholamines. However, evidence for depletion of myocardial intracellular potassium in subarachnoid haemorrhage is only indirect, where a decrease in total body potassium, not reflected in serum levels, has been demonstrated. There is, therefore, much evidence to suggest that catecholamines are responsible for electrocardiographic abnormalities and myocardial lesions found in the human subject with subarachnoid haemorrhage, and that these changes are potentiated by increased corticosteroid activity which leads to loss of myocardial intracellular potassium.

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