When symptoms of malacia become manifest in a hypophosphataemic patient histological confirmation of the diagnosis should be obtained and early aggressive treatment of the condition undertaken to prevent the rapid development of disabling bone disease. Aluminium hydroxide should be temporarily withdrawn and vitamin D should be given. Withdrawal of aluminium hydroxide may, by itself, be sufficient[23] but as these patients are likely to be suffering from abnormalities of vitamin D metabolism also[24] some form of vitamin D seems indicated. In addition, Jones[17] showed that hypophosphataemic rickets in rats could be prevented or cured by vitamin D.

References

[1] Pendras, J P, and Erickson, R V, Annals of Internal Medicine, 1966, 64, 293.
[2] Mallick, N P, and Berlyne, G M, Lancet, 1968, 2, 1316.

[3] Lotz, M, Zisman, E, and Bartter, F C, New England Journal of Medicine, 1968, 278, 409.
[4] Lichtman, M A, Miller, D R, and Freeman, R B, New England Journal of Medicine, 1969, 280, 240.
[5] Bishop, M C, Ledingham, J G G, and Oliver, D O, Proceedings of the European Dialysis and Transplant Association, 1971, 8, 106.
[6] Bloom, W I, and Flinchum, D, Journal of the American Medical Association, 1960, 174, 1327.
[7] Senior, B, American Journal of Diseases of Children, 1973, 125, 442.
[8] Garrick, R, Ireland, A W, and Posen, S, Annals of Internal Medicine, 1971, 75, 211.
[9] Zettner, A, and Seligson, D, Clinical Chemistry, 1964, 10, 869.
[10] Technicon Instruments Corporation, Chauncey, New York, 1960.
[11] Young, D S, Journal of Clinical Pathology, 1966, 19, 397.
[12] Morgenstern, S, et al, Clinical Chemistry, 1965, 11, 876.
[13] Kleerekoper, M, et al, Clinical Chemistry, 1974, 20, 369.
[14] Greulich, W W, and Pyle, S I, Radiographic Atlas of Skeletal Development of the Hand and Wrist, 2nd edn. Stanford, Stanford University Press, 1959.
[15] Garrick, R, Doman, P, and Posen, S, Clinical Science, 1972, 43, 789.
[16] Fournier, A E, et al, Journal of Clinical Investigation, 1971, 50, 592.
[17] Deobald, H J, and Elvehjem, C A, American Journal of Physiology, 1935, 111, 118.
[28] Jones, J H, American Journal of Physiology, 1938, 124, 230.
[19] Freeman, S, and McLean, F C, Archives of Pathology, 1941, 32, 387.
[20] Ingham, J P, Stewart, J H, and Posen, S, British Medical Journal, 1973, 2, 745.
[21] Bishop, M C, et al, British Medical Journal, 1972, 3, 664.
[22] Pierides, A M, et al, British Medical Journal, 1976, 1, 190.
[23] Baker, L R, et al, British Medical Journal, 1974, 3, 150.
[24] De Luca, H F, Journal of Laboratory and Clinical Medicine, 1976, 87, 1.

Immediate plasma renin response to propranolol: differentiation between essential and renal hypertension

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Summary

The immediate short-term effect on plasma renin activity of intravenous injection of propranolol was studied in 31 normal subjects and 166 hypertensive patients. In patients with essential hypertension and normal subjects plasma renin activity fell considerably within 15 minutes; the fall was directly proportional to initial plasma renin levels. In contrast, in patients with renal hypertension the fall was much less pronounced or totally absent. These differences in response to propranolol provide, though presently only on a group basis, a biochemical means of differentiating between patients with renal hypertension and those with essential hypertension. The observations also indicate that, unlike normal subjects and patients with essential hypertension, in patients with renal hypertension sympathetic activity plays no part in the control of basal plasma renin levels.

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Introduction

Precision in endocrine diagnosis depends on the ability to measure all components of the feedback loops controlling hormone secretion.[1] Nevertheless, renin levels in hypertensive patients are commonly still being interpreted without consideration of renal perfusion pressure, sodium concentration at the macula densa, or sympathetic tone at the juxtaglomerular apparatus, these probably being the main factors controlling renal renin release.[2] None of the components of the feedback loops by which renin secretion is controlled is easily measurable in clinical practice. In an attempt to quantify sympathetic tone at the juxtaglomerular apparatus we have taken the immediate effect of acute beta-receptor blockade on basal plasma renin activity (PRA) as an indication of the extent to which renin release under basal conditions is mediated by the sympathetic nervous system. A preliminary account of part of this work has been published.[3]

Patients and methods

We studied (a) 31 normal volunteers (19 female and 12 male hospital employees), (b) 102 patients (61 women) with stable benign essential hypertension (WHO stage 1 and 2), (c) 58 patients (30 women) with well-established renal hypertension of comparable duration and severity caused by chronic parenchymatous renal disease, and (d) six patients (two women) on chronic intermittent haemodialysis with hypertension of terminal renal failure.

Clinical details of the subjects are given in table I. Essential hypertension was diagnosed only after secondary forms of hypertension had been excluded by the usual diagnostic tests, which included urine analysis, blood chemistry, intravenous rapid-sequence

TABLE I—*Age, known duration of hypertension, 24-hour urinary sodium excretion (mean and range), PRA values, pulse rate, and blood pressure (mean ±1 S D) in normal subjects and patients with hypertension. Significances of differences are also given*

| | Normal subjects | | Patients with essential hypertension | | Patients with renal hypertension | | | | | |
| | | | | | Without renal failure | | With renal failure | | Combined | |
	Values	P values	Values	P values	Values	P values	Values	P values	Values	P values
No of subjects	31		102		32		32		64	
Age (years)	26·6 (20–35)		37·5 (15–67)		39·4 (17–72)		36·5 (16–72)		38·0 (16–72)	
Known duration of hypertension (months)			48·9 (1–240)		54·1 (1–240)		88·1 (3–240)		70·9 (1–240)	
24-Hour urinary sodium excretion (mmol/24 h)	156·2 (55–240)		166·5 (55–240)		144·6 (52–285)		124·0 (50–326)		142·0 (50–326)	
Log PRA (ng AI/l h):										
Basal	2·41 ± 0·41	<0·001	2·24 ± 0·46	<0·001	2·44 ± 0·45	<0·05	2·49 ± 0·51	NS	2·47 ± 0·47	<0·01
After propranolol	2·29 ± 0·37		2·13 ± 0·41		2·40 ± 0·43		2·48 ± 0·50		2·44 ± 0·47	
Pulse rate min:										
Basal	65·5 ± 11·4	<0·001	75·2 ± 13·5	<0·001	70·7 ± 10·0	<0·001	72·9 ± 10·9	<0·001	71·8 ± 10·4	<0·001
After propranolol	55·9 ± 9·2		62·3 ± 9·7		59·8 ± 8·1		63·9 ± 8·7		61·8 ± 8·7	
Blood pressure (mm Hg):										
Basal	96·5 ± 10·1	NS	131·1 ± 20·9	<0·001	136·0 ± 24·6	NS	138·1 ± 19·6	<0·01	137·0 ± 22·1	<0·05
After propranolol	97·3 ± 8·3		128·0 ± 23·1		137·8 ± 28·4		134·4 ± 18·6		136·1 ± 23·9	

pyelography, determination of urinary catecholamines (in all patients), and renal arteriography (in patients under 35 years). The diagnoses of the patients with renal hypertension were: chronic bilateral pyelonephritis (16); chronic unilateral pyelonephritis (5); chronic glomerulonephritis, histologically confirmed (24); polycystic kidney disease (4); analgesic nephropathy (3); diabetic glomerulosclerosis (3); bilateral nephrocalcinosis and nephrolithiasis (1); and dysplastic kidneys (2). Thirty-two patients had normal serum creatinine levels; in 26 patients serum creatinine ranged from 159 to 707 μmol/l 1·8 to 8 mg/100 ml). None of the patients had evidence of renal salt wasting or nephrotic syndrome.

All subjects were on an unrestricted (home) intake of sodium and potassium; hypertensive patients had stopped all medication at least two weeks before investigation. This seems to be a sufficiently long drug-free period.[4 5] Forty-eight patients with essential hypertension and 38 with renal hypertension had never received any antihypertensive medication. Patients with evidence of congestive heart failure, atrioventricular block, or a history of bronchial asthma, and those receiving oral contraceptives or spironolactone were excluded from the study. The day before the study a 24-hour urine collection was started for determining urinary sodium excretion. After an overnight fast and at least one hour's supine bed rest 5 ml of blood for the determination of PRA was taken between 8 am and 10 am. Propranolol 5 mg was immediately administered intravenously over two minutes. Fifteen minutes after the beginning of the injection a second blood sample for determining PRA was taken. Blood pressures and pulse rates were recorded at the time the blood samples were withdrawn. In our experience and in that of others,[6] one hour's bedrest is sufficient time to achieve basal PRA levels. The short interval of 15 minutes between the two samples was chosen to reduce any spontaneous variation of PRA.[7] At the same time, this period should permit significant induced changes of PRA to occur, since it approximates to the normal half life of PRA.[8-10] In six normal subjects the study was repeated two weeks later, but 5 ml of 0·9% saline was injected instead of propranolol.

PRA was determined by radioimmunoassay by the method of Boyd et al.[11] In our laboratory the intra-assay coefficient of variation for repeat determinations is ±4%. This figure agrees closely with that reported by Boyd et al.[11] With the given reproducibility, only changes in PRA greater than 10% were considered to be significant. Propranolol added to plasma samples before incubation did not affect PRA determination tested at concentrations of up to 20 mg/l.

Standard methods were used for calculating means, standard deviations, and correlation coefficients; the difference in means between groups was assessed using Student's *t* test.

Results

The means (±SD) of basal and post-propranolol values of PRA, pulse rate, and blood pressure are shown in table I. Significant correlations between the different measurements are shown in table II. Within the given range of 24-hour urinary sodium excretion no significant correlation between sodium excretion and PRA was observed in either normal or hypertensive subjects. The frequency distribution of basal PRA in normal subjects and in patients with essential and renal hypertension is shown in fig 1. This figure includes the values of 11 normal subjects in whom only basal PRA measurements were available.

TABLE II—*Correlations between basal PRA and change in PRA after propranolol age, and known duration of hypertension.*

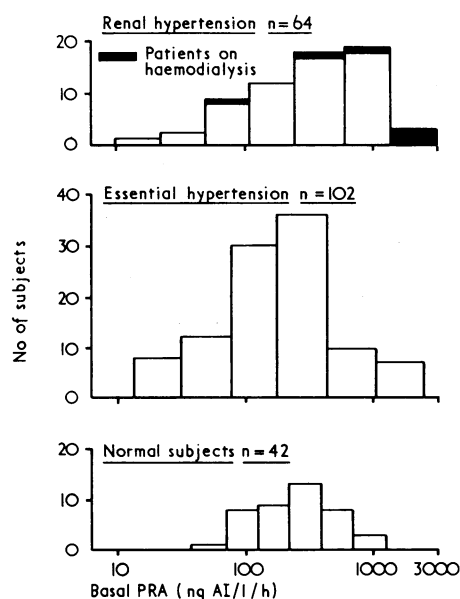| Correlations | Normal subjects | | Patients with essential hypertension | | Patients with renal hypertension | |
	r	P	r	P	r	P
Log basal PRA v difference in PRA (%) after propranolol	−0·65	<0·001	−0·62	<0·001	−0·23	NS
Age v log PRA			−0·46	<0·001	−0·32	<0·01
Known duration of hypertension v log PRA			−0·20	<0·05	0·02	NS

FIG 1—Distribution of basal plasma renin activity in hypertensive patients and normotensive controls. A log-normal distribution was confirmed by the Kolmogoroff-Smirnoff test only for normal subjects and patients with essential hypertension.

Response of PRA to propranolol in normal subjects—In normal subjects PRA decreased by up to 42% within 15 minutes (fig 2). The percentage decreases in PRA were significantly related to basal levels (see table II). PRA remained unchanged in six normal subjects after the administration of 0·9% saline.

Response of PRA to propranolol in hypertensive patients—Fig 3 shows the response of PRA to intravenous propranolol in patients with stable essential and renal hypertension, the subjects again being grouped according to their basal level of PRA. PRA fell significantly after propranolol in those patients with essential hypertension whose basal PRA was greater than 100 ng angiotension I/l/hour, the percentage decrease again being related to basal PRA (table II). In contrast, the fall in PRA after propranolol in patients with renal hypertension was
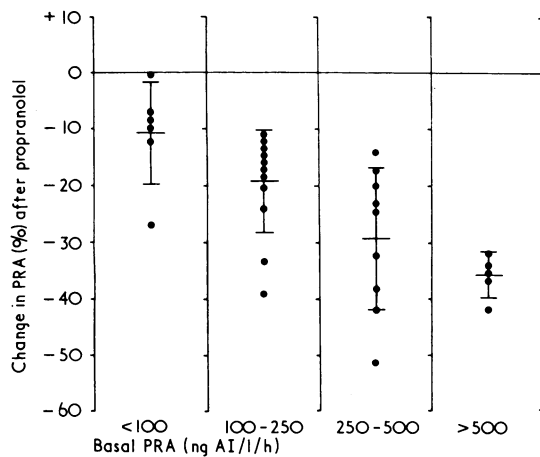
FIG 2—Mean fall ($\pm$ SD) in PRA 15 minutes after intravenous administration of 5 mg propranolol in 31 normal subjects, grouped according to their basal levels of PRA.
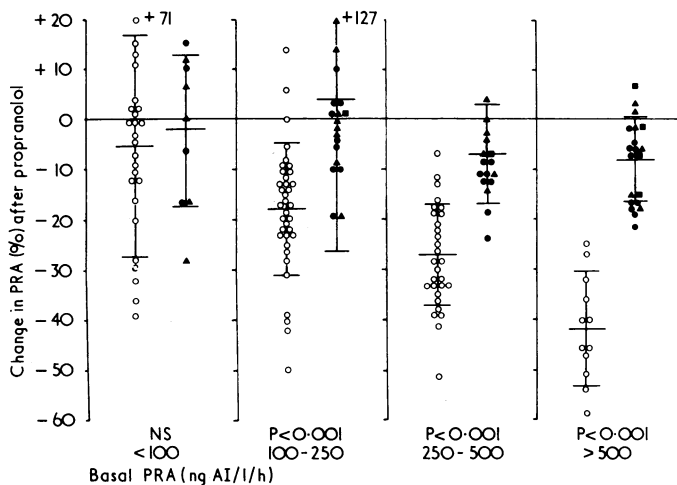

FIG 3—Changes in PRA 15 minutes after the intravenous administration of 5 mg propranolol in 102 patients with essential hypertension (O), 64 patients with renal hypertension from chronic parenchymatous renal disease with normal (●) and raised (▲) serum creatinine. ■=Patients on chronic intermittent haemodialysis.

uniformly less pronounced or absent. There was no correlation between basal PRA and the magnitude of decrease after propranolol (table II).

The pulse rate after propranolol decreased similarly in all subjects investigated; blood pressures did not change appreciably in any of the groups (table I).

Discussion

Propranolol inhibits the rise in PRA induced by orthostasis or by acute or chronic administration of diuretics in normal subjects and in patients with essential hypertension.[12-14] The present study shows that propranolol also acutely lowers the previously unstimulated "basal" PRA after supine bed rest.

Since it is accepted that the fall in PRA after acute administration of propranolol is due to the inhibition of renin release,[14 15] the magnitude of the decrease of PRA in our experiments seems to depend on two factors: the disappearance rate of renin activity from the circulation; and the extent to which basal release of renin is mediated by sympathetic tone. Given a half life of PRA of between 10 and 15 minutes,[8-10] the fall in PRA should not exceed 50% after 15 minutes, even if PRA after supine rest were maintained solely by sympathetic activity. The maximum fall in PRA of between 50 and 60% observed in our study agrees with this. The highly significant correlation between

basal PRA levels and the magnitude of decrease after propranolol suggests that sympathetic tone (sympathetic renal nerve activity or the level of circulating catecholamines, or both) is a major determinant of basal PRA in normal subjects as well as in patients with stable essential hypertension. No correlation has been observed between plasma noradrenaline levels and PRA[16]; since, however, plasma noradrenaline has not been shown to reflect the total sympathetic input to the kidney, our interpretation is still valid.

Since the rate of fall in PRA after propranolol in patients with "high-renin" essential hypertension approximates to the maximal possible decrease, taking into account the half life of PRA, high basal PRA in benign essential hypertension may be maintained by increased sympathetic tone. This may explain the better hypotensive effect of propranolol in patients with high renin levels.[17 18]

Since we could not show any substantial fall in PRA after propranolol in patients with renal hypertension even after prolonged intervals,[19] it seems that an impaired removal of PRA from the circulation[19 20] is not the major explanation for the difference in response of PRA to propranolol between those with essential and those with renal hypertension. Furthermore, there is no evidence of a generally impaired responsiveness of the sympathetic nervous system in patients with renal hypertension. The effect of propranolol on the cardiac beta-receptors seems to have been comparable in normal subjects and in patients with essential and renal hypertension, as judged by the similar decreases in pulse rate in the three groups (table I). Hence basal PRA in patients with renal hypertension seems to be maintained largely by factors other than sympathetic tone. The reduced renal perfusion, common to all patients with renal hypertension, might indicate that the renal baroreceptors are responsible for mediating renin release.

One of the critical questions that arise from this study is whether the patients with benign essential hypertension had secondary hypertensive renal damage, which might have obscured any differences between essential and renal hypertension. Since the progressive renal abnormality produced by long-standing hypertension apparently results in "low-renin" hypertension,[21 22] patients with long-standing essential hypertension should be found in the low-renin group, where no difference in the plasma renin response between essential and renal hypertension was observed. This is confirmed by the significant negative correlations between age, known duration of hypertension, and PRA observed in this series (table II). If patients with more advanced essential hypertension, in whom the onset of renal failure might be associated with a final rise in PRA again,[23] had been included in our study we would not have expected to observe a difference between such patients and those with renal hypertension.

Plasma renin measurements in patients with essential and renal hypertension give values which range from low to very high levels (fig 1) and there is nothing to suggest that these two types of hypertension can be differentiated by measuring basal PRA alone. Nevertheless, the present study shows that on a group basis the immediate renin response to propranolol differentiates between patients with essential hypertension and those with renal hypertension. This differentiation may become diagnostically useful, for instance by optimising the time interval between sampling or by simultaneous consideration of the other components of the feedback loops controlling renin secretion.

References

[1] Parfitt, A M, Clinics in Endocrinology and Metabolism, 1974, 3, 454.
[2] Davis, J O, American Journal of Medicine, 1973, 55, 333.
[3] Skrabal, F, Klinische Wochenschrift, 1975, 53, 629.
[4] Lebel, M, et al, Lancet, 1974, 2, 308.
[5] Morgan, T O, et al, Journal of Clinical Pharmacology, 1975, 2, 159.

[6] Pettinger, W A, and Mitchell, H C, New England Journal of Medicine, 1975, 292, 1214.

[7] Katz, F H, et al, Journal of Clinical Endocrinology and Metabolism, 1975, 40, 125.

[8] Michelakis, A M, and Mizukoski, H J, Journal of Clinical Endocrinology, 1971, 33, 27.

[9] Christlieb, A R, et al, Proceedings of the Society for Experimental Biology and Medicine, 1968, 128, 841.

[10] Skrabal, F, and Czaykowska, W, Klinische Wochenschrift, 1974, 52, 1173.

[11] Boyd, G W, et al, Lancet, 1969, 1, 213.

[12] Winer, N, et al, Clinical Endocrinology, 1969, 29, 1168.

[13] Michelakis, A M, and McAllister, R G, Journal of Clinical Endocrinology and Metabolism, 1972, 34, 386.

[14] Bravo, E L, Tarazi, R C, and Dustan, H B, Journal of Laboratory and Clinical Medicine, 1974, 83, 119.

[15] Sullivan, J M, Adams, D F, and Hollenberg, N K, Clinical Research, 1973, 21, 453.

[16] Louis, W J, et al, Circulation Research, 1974, 35, suppl No 1, p 57.

[17] Bühler, F R, et al, New England Journal of Medicine, 1972, 287, 1209.

[18] Karlberg, B E, et al, British Medical Journal, 1976, 1, 251.

[19] Skrabal, F, et al, Nieren und Hochdruckkrankheiten, 1976, 5, 1.

[20] Brown, J J, et al, Nephron, 1969, 6, 329.

[21] Brown, J J, et al, Lancet, 1974, 2, 320.

[22] Padfield, P L, et al, Lancet, 1975, 1, 548.

[23] Schalekamp, M A, et al, Ciba Symposium on Hypertension, Malta 1974, p 147. Horsham, Ciba Laboratories, 1975.

Enhanced drug metabolism in cigarette smokers

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Summary

The effect of cigarette smoking on salivary antipyrine disappearance rate, and as an index of hepatic drug metabolism, was studied in 42 healthy subjects. Antipyrine half life was significantly shorter in smokers compared with non-smokers. To determine whether this difference was due solely to tobacco consumption eight subjects were restudied two months after they stopped smoking. The mean antipyrine disappearance rate in this group increased by 23% in contrast to that of a control group, which did not alter. Cigarette smoking contributes to the considerable variation in interindividual rates of drug metabolism.

Introduction

Antipyrine is metabolised almost completely by the liver.[1][2] Since it is not appreciably bound to plasma proteins and is distributed evenly throughout the total body water, the rate of antipyrine elimination provides a suitable method of assessing the activity of hepatic microsomal drug-oxidising enzymes. The wide variation in plasma antipyrine disappearance rates in normal subjects[2][3] reflects the well-recognised phenomenon of large differences in rates of drug metabolism among apparently healthy individuals. While genetic factors are important in determining this variability[3][4] there is increasing evidence that other factors such as age, sex, drug ingestion, and exposure to environmental agents are also relevant.[4-10]

One environmental factor that has received comparatively little attention as a potential stimulant of hepatic drug metabolism is cigarette smoking. For example, increased activity of aryl hydrocarbon hydroxylases has been observed in the placenta and pulmonary alveolar macrophages after smoking.[11][12] Clinical studies in smokers have shown decreased pharmacological effects of pentazocine,[13] propoxyphene,[14] and benzodiazepines.[14] Although a recent study has provided more direct evidence that smoking stimulates drug metabolism by showing increased antipyrine clearance rates in smokers,[6] these results varied considerably according to the age and other characteristics of the patients and could not be attributed solely to cigarette smoking. Smoking had no effect on diazepam plasma disappearance.[15] Furthermore, although plasma levels of phenacetin are considerably lower in smokers than in non-smokers after comparable oral doses, there is no change in the plasma disappearance rate, and this probably reflects factors other than enhanced hepatic drug metabolism.[16]

We report here the results of a study designed to assess the effect of cigarette smoking on drug metabolism and to exclude both the influence of genetic variability and the effects of other environmental agents. This was done by studying a group of smokers before and after they had stopped smoking.

Patients and methods

The subjects studied were all healthy volunteers, some of whom were attending a hypnotherapy "stop-smoking" clinic. All gave informed consent. Subjects were excluded from the study if there was evidence of liver or renal disease or other disorders known to influence hepatic drug metabolism.[17-20] Each volunteer was carefully questioned about his consumption of tobacco, alcohol, tea, and coffee and his use of pharmaceutical agents that may influence antipyrine half life. Those taking known hepatic microsomal enzyme-inducing drugs were excluded, as were those consuming alcohol in moderate amounts (< 50 g ethanol per day). Most smokers smoked more than 20 cigarettes per day, but all consumed at least 11 cigarettes a day or 60-85 g (2-3 oz) tobacco a week. The non-smokers had not smoked at all for the previous six weeks. The average age of the smokers was 39 years (range 16-63 years) and that of the non-smokers 35 years (range 20-63 years). The subjects in each group were comparable in sex and consumption of coffee, tea, and alcohol.

Plasma or saliva antipyrine half lives, or both, were studied in 42 subjects (17 non-smokers and 25 smokers). Several people were studied more than once to assess intraindividual variability and any difference in apparent antipyrine half life due to different routes of drug administration (oral as opposed to intravenous) or method of sampling (saliva as opposed to plasma). Repeat studies were carried out in a manner identical to the initial studies. Eight smokers were also restudied about two months after they had stopped smoking. These subjects were then asked about changes in their life style other than stopping smoking.

An aqueous solution of antipyrine in a dose of 10 mg/kg body weight was either injected intravenously over 10 minutes or taken by mouth dissolved in 100 ml of orange juice. Five or more samples of venous blood (10 ml) or fresh saliva (5 ml) were collected at intervals during the next 30 hours. The antipyrine concentration of each sample was

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