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Determination of glomerular filtration rate by controlled infusion of ^{51}Cr-EDTA.

A preliminary study.

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The aim of the investigation was to study the kinetics of ^{51}Cr-EDTA in order to develop a technique for the determination of its renal clearance during steady state conditions. We calculated the plasma clearance of ^{51}Cr-EDTA from infusion rate and plasma concentration. In order to obtain stationary conditions rapidly, external measurement and controlled infusion were used.

Patients

Nine patients were studied, aged 25 - 59 years. Three were evaluated as prospective kidney donors. Six had known or suspected renal disease. Renal function was normal or near normal in eight, and moderately impaired in one.

Three of the patients were studied in preliminary experiments after a single injection of ^{51}Cr-EDTA. In the remaining six controlled infusion of ^{51}Cr-EDTA was used. In two of these bladder urine was collected.

Methods

The subjects were semi-recumbent in a reclining chair, except in two experiments with bladder catheter, when they lay supine. One detector (2 inch diameter sodium iodide crystal with photomultiplier, with cylindrical lead collimation extending 1 cm beyond surface of crystal) was placed at the top of the skull. A second identical detector was positioned over the heart perpendicular to the chest wall and close to the skin, but not interfering with respiratory movements.

^{51}Cr-EDTA (ethylene-diamine-tetra-acetic acid labelled with ^{51}Cr, The Radiochemical Centre, Amersham, England) was injected or infused through a plastic catheter or cannula in an antecubital vein. The total dose administered was usually 200 - 300 µCi. In the infusion experiments, approximately 200 µCi was first injected during approximately one minute (priming dose), followed by infusion at a slower rate (see below).

Blood samples were collected at intervals of 5 to 15 minutes from a venous cannula in the opposite arm, except in two experiments where an arterial cannula was used. In these two experiments urine was collected from an indwelling bladder catheter, and conventional inulin- and PAH-clearance determinations were made simultaneously. The inulin and PAH infusion was separate from the infusion of ^{51}Cr-EDTA. In the other experiments urine was not collected.

Each blood sample (usually approximately 6 ml) was collected in a heparinized glass tube. After centrifugation, 2 ml plasma was transferred to another glass tube and counted in well crystal scintillation counter. At least 3000 counts were taken. Unless otherwise stated, radioactivity is given in diagrams and tables as counts per second (cps) in 2 ml. Aliquots of solutions injected were counted, after appropriate dilution, in exactly the same way.

In four patients (No. 1 - 4) glomerular filtration rate was measured by single injection of ^{51}Cr-EDTA (Bröchner-Mortensen, 1972) two days before the infusion experiment. In patient No. 6 GFR was measured 6 weeks before the infusion experiment.

Each of the two detectors was connected to a pulse analyzer (Wallac AS-11) and the pulses were recorded on a 4-channel tape recorder. The pulse rates were shown on a strip chart recorder (Honeywell class 194).

In the controlled infusion experiments (fig. 1), the precordial pulse rate signal, y, was fed into a proportional controller programmed on a small analog computer. The controller output signal, u, was thus defined according to

$$u = V_o - K\ (y - cps_d) \qquad (1)$$

where V_o is a basic infusion rate. K is a gain constant and cps_d is a desired pulse rate. Values for V_o, K, and cps_d were preset before the experiment.

After voltage to pulse frequency conversion in a circuit described by Hood (1970), u controlled a stepping motor driven infusion machine (Inforce) with a 50 ml all glass syringe.

The stepping motor pulses were recorded on the third channel of the tape recorder (fig. 1) and also counted during 15 min intervals using a counter. The total volume infused (approximately 50 - 200 ml) depended on, i.a., the patient's renal function and the chosen cps_d. While emptied syrings were replaced, the infusion was stopped for approximately 1.5 minutes.

Preliminary studies

In preliminary work possible mathematical models containing two or three compartments were assumed using typical values for compartment volumes and connecting flows, or time constants (fig. 2).

The eigenvalues of the model for different clearance values were compared with k-values obtained by fitting three exponentials to single injection experiments with frequent plasma concentration measurements (White unpublished). Although a good curve fitting may be obtained for considerably different k-values the resemblance between model and patient data was reasonable. The slowest exponential indicated in some cases that the total distribution volume was slightly underestimated in the model.

The clearance value correction suggested by Bröchner-Mortensen (1972) in order to account for the error made when assuming a one-pool system, gave correct clearance values if used for the model. As was found by Bröchner-Mortensen (1972) the disregarded area under the concentration curve was approximately constant for different clearance values, for identical flows and volumes. The relation between the disregarded and the total area was in accordance with Bröchner-Mortensen (1972), so that if the volumes in the model were slightly too low then the flows were also too low.

Single injection, constant infusion and controlled infusion experiments on the model were simulated using the simulation

program SIMNON for the PDP-15 digital computer at the Division of Automatic Control. The final slope of the plasma curve in the single injection simulations was attained after less than one hour, which is slightly shorter time than in most experiments (White unpublished).

Constant infusion simulation yields that steady state is obtained in about one and a half hour provided that a well matched priming dose is given. The value of this dose is critical particularly for low renal function. The model has for instance for clearance 18 ml/min a slowest timeconstant of approximately 14 hours. Estimates of clearance based on infusion rate and plasma concentration using a constant infusion experiment would thus require long duration. In order to avoid this some regulator should be used.

The simple proportional controller in eq (1) with the plasma-concentration as y was simulated, and the steady state was attained slightly faster than without control, if V_o and cps_d as well as the priming dose were well matched. If V_o was 30 % too low, the settling time was decreased from four hours to one and a half hour by the controller with a reasonable gain constant K (Cl = 120 ml/min). The model was thus used to indicate that using plasma concentration measurements a correct clearance value would be obtained after say two hours without any urine collection even if the priming dose and the infusion rate were mismatched.

If the gain of the controller was increased giving "tighter" control, the plasma concentration would be constant very soon,

but it would take longer to get steady state in the whole system, and the measurement noise would be magnified making the infusion rate difficult to define.

No plasma concentration measurements were however available for the controller, only the external measurements of for instance precordial activity.

Two preliminary experiments were done. The external activities were recorded after a single injection. The slope of the plasma and the precordial signals during the fourth hour were compared (table 1). The differences in $T_{1/2}$ indicate that all compartments of the body do not behave uniformly even after four hours. Some very slow pools of minor importance for the plasma curve may give a significant contribution to the precordial curve. The curves may require another four hours to become parallel in the lin log diagram. These slow pools are not accounted for in the assumed compartment model.

Another disadvantage with the external measurements is that it is more difficult to match V_o and cps_d because of the influence of the geometry on the external signal.

Results

Plasma concentration, precordial count rate and infusion rate are shown in diagrams, one for each of the six patients who recieved controlled infusions. The recordings of precordial count rate and

of infusion rate showed considerable "statistical" fluctuations in the original tracings. The original precordial count rate curve was "smoothed" by hand when drawn into the diagrams. The corresponding infusion rate curve was not used in the diagrams. Instead, the total number of counts was noted at 15 min intervals, and the average during each interval is presented in the diagrams. (This procedure was occasionally checked by replay of the tape recording of the original signal.)

Count rate from top of the skull (not included in the diagrams) was generally lower than the precordial count rate, and the initial decline of the curve was less steep over the skull than over the heart. However, a detailed analysis of these and other findings in the skull tracings was impossible, since movement artifacts could not be avoided.

The diagrams show that both plasma concentration and precordial count rate tended to approach a rather constant level after 30 - 40 minutes. (The precordial tracing sometimes showed a small, barely significant, rising trend after the rapid initial decline.) Patient No. 3 was exceptional in that constant levels were not reached until much later, which probably reflected his impaired renal function.

The infusion rate did not regularly reach a constant level. Patterns varied between subjects. In patients No. 4, 5, and 6 (possibly also No. 2) the infusion rate was slower after approximately 60 minutes than during the preceding period.

In the longest experiments a slight decrease in the plasma curve started after approximately 150 minutes without a corresponding decrease in the precordial curve, which in fact showed a small rising trend.

Plasma clearance values calculated from the later parts of the experiments differed moderately but not systematically from the preceding determinations of GFR (table 1). Renal clearance was measured in two patients and was 31 ml/min lower than the simultaneous plasma clearance, i.e. the indicator was infused at a higher rate than that at which the indicator was excreted by the kidneys.

Discussion

The constant or nearly constant levels of radioacitivity in the plasma and over the heart during the later phases of the infusion experiments indicated that a "steady state" was reached. However, the variations in infusion rate demonstrated that true stationary conditions were not present. We cannot offer a complete explanation for the findings, partly because of the variations in individual patterns and the limited number of experiments. But we will discuss briefly the combination of (nearly) constant precordial and plasma activity with declining infusion rate and lower renal than plasma clearance, a pattern suggested in some of the experiments.

Plasma delivered indicator to tissues at an unknown rate, and to the kidney at a constant rate. Plasma received indicator from

tissues at an unknown rate, and from the infusion at a declining rate, greater than the renal excretion. This must mean that the balance of exchange between plasma and tissues in these experiments was such that there was a decreasing net transport to tissues in general from the plasma. Such tissues would not have been "loaded" with radioactivity in the early phases of the experiment when the plasma concentrations were high, and would continue to take up radioactivity from the plasma even after one or two hours.

As the precordial detector did not indicate any corresponding net uptake it is possible that the tissues under the detector no longer took up radioactivity. It is also a consequence of the controller, which tried to keep precordial activity constant. The very late decrease in plasma activity also indicates this. When the slow pools, discussed after the single injection experiments, were filling up, the detector signal increased slightly, the controller reacted, the infusion rate decreased and the plasma concentration began to decrease.

The present experiments indicated a constant plasma radioactivity, but not stationary conditions in the body as a whole. Therefore, calculation of plasma clearance from infusion rate did not permit an estimation of renal clearance under these circumstances. It is conceivable that, if the experiments had been prolonged further, infusion rate may have stabilized at a lower level. This would mean a lower plasma clearance, possibly identical to the simultaneous renal clearance.

It may be noted that the patient (No. 3) who most markedly

deviated from the pattern discussed above, and who showed a rising and then constant infusion rate, had a plasma clearance identical to the previously measured GFR.

Plasma clearance of Diodrast (iodopyracet) and Hippuran (ortho-iodo-hippurate) can be used to obtain a measure of the renal clearance (Christiansen et al. 1970; Gagnon et al. 1970). These indicators are excreted much more rapidly than ^{51}Cr-EDTA. External measurements and plasma disappearance of iothalamate, an indicator treated by the kidneys like ^{51}Cr-EDTA, do not give correct values for the renal clearance (Cohen et al. 1971). On the other hand, plasma clearance of inulin during prolonged infusion may give a good measure of inulin renal clearance (Cole et al. 1972). It may be relevant that, although inulin and ^{51}Cr-EDTA have the same renal clearance, they behave quite differently in the body as a whole, where the distribution volume of ^{51}Cr-EDTA is much larger than that of inulin (Ladegaard-Pedersen & Engell, 1972).

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Table 1

^{51}Cr-EDTA single injection. Plasma samples and precordial detector.

Patient		A	B
Weight		75 kg	70 kg
Body surface area		1.95 m^2	1.67 m^2
Clearance		116 ml/min	114 ml/min
Fourth hour slope	plasma	89 min	114 min
($T_{1/2}$)	precordial	120 min	168 min

Table 2

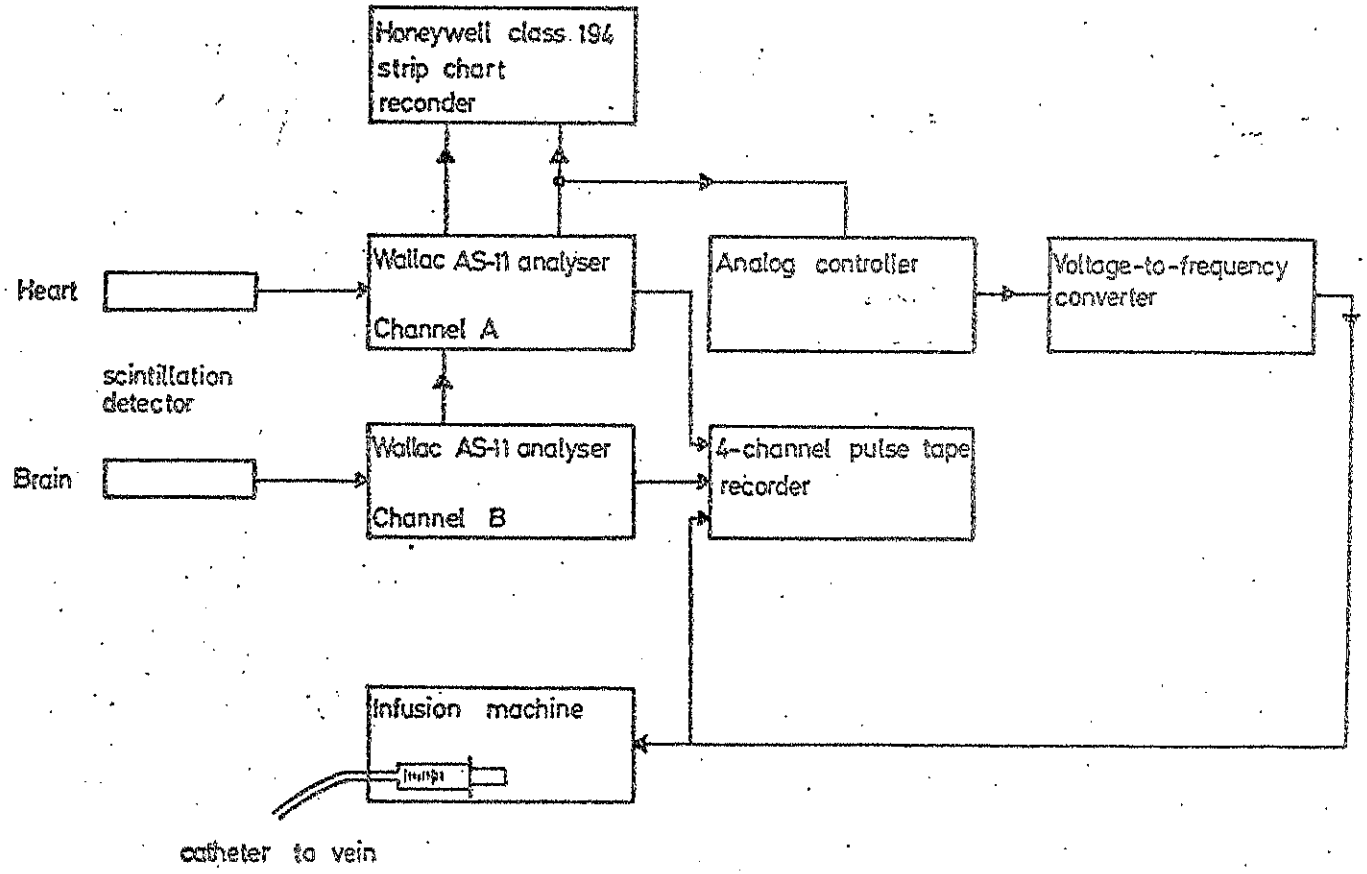
Controlled infusion of ^{51}Cr-EDTA

Pat.No.	Sex	Weight (kg) Body surface area (m^2)	GFR (ml/min)	Controlled infusion	
				Renal clearance (ml/min)	Plasma clearance (ml/min)
1	F	52 1.48	73	-	83 x)
2	F	75 1.86	107	-	120
3	M	71 1.84	48	-	48
4	F	57 1.55	88	-	84 (74) xx)
5 xxx)	M	71 1.91	-	109	140
6 xxx)	F	57 1.50	137	109	140

x) During 45 - 60 min.

xx) Lower value measured during last 45 min. Higher value during preceding periods excluding last 30 min.

xxx) Prospective kidney donor.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4-channel pulse tape
recorder
Infusion machine
catheter to vein

fig 1.

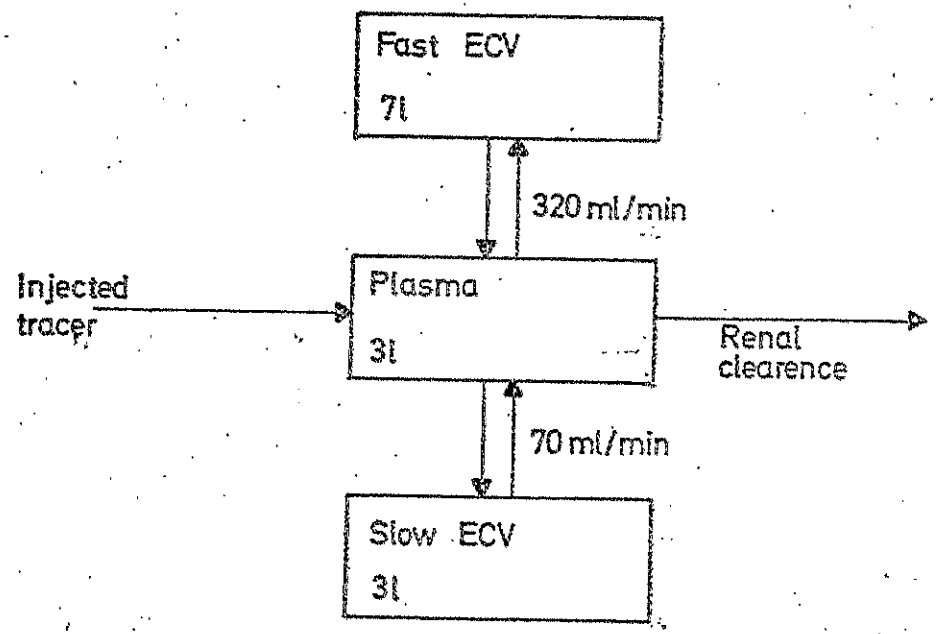
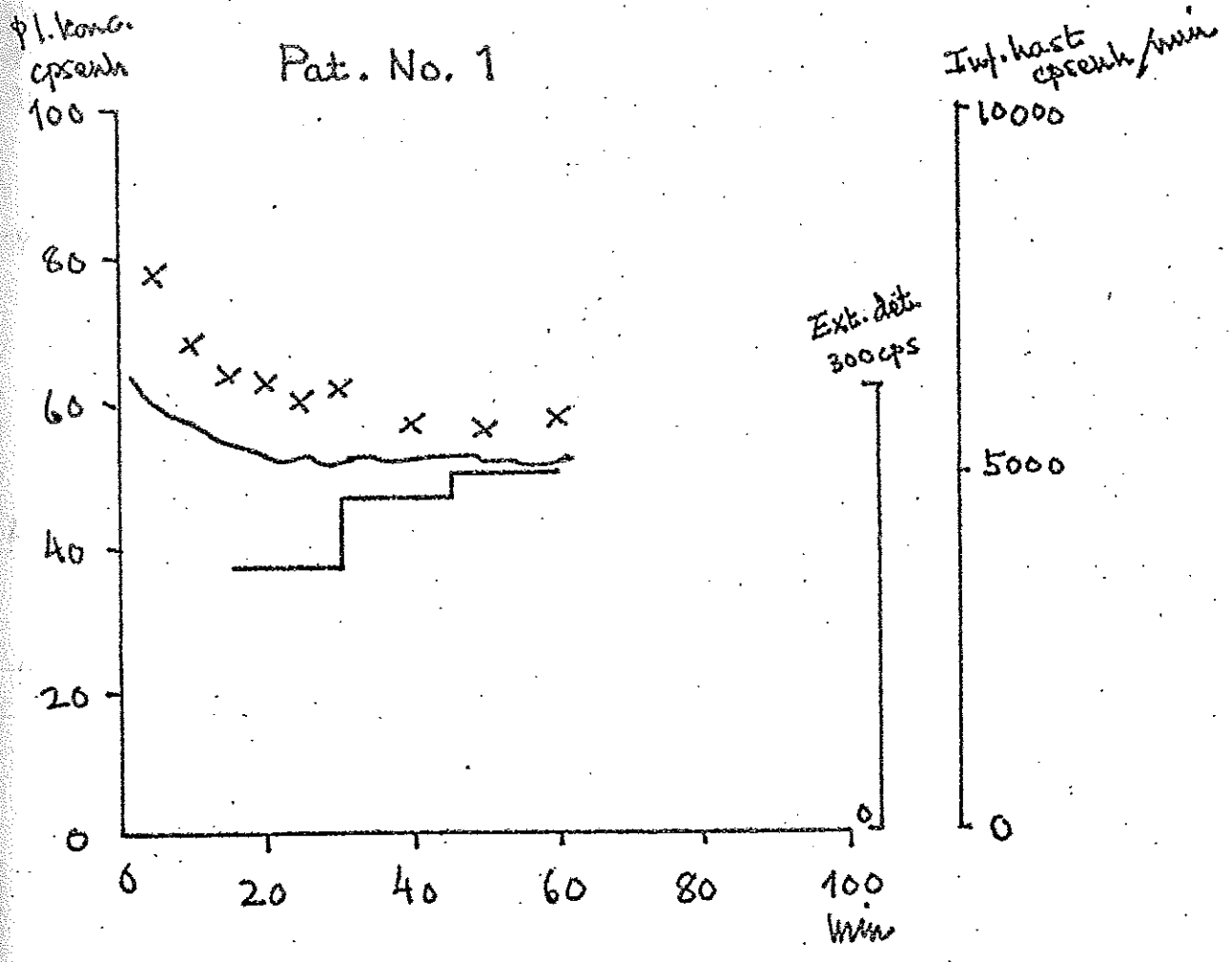


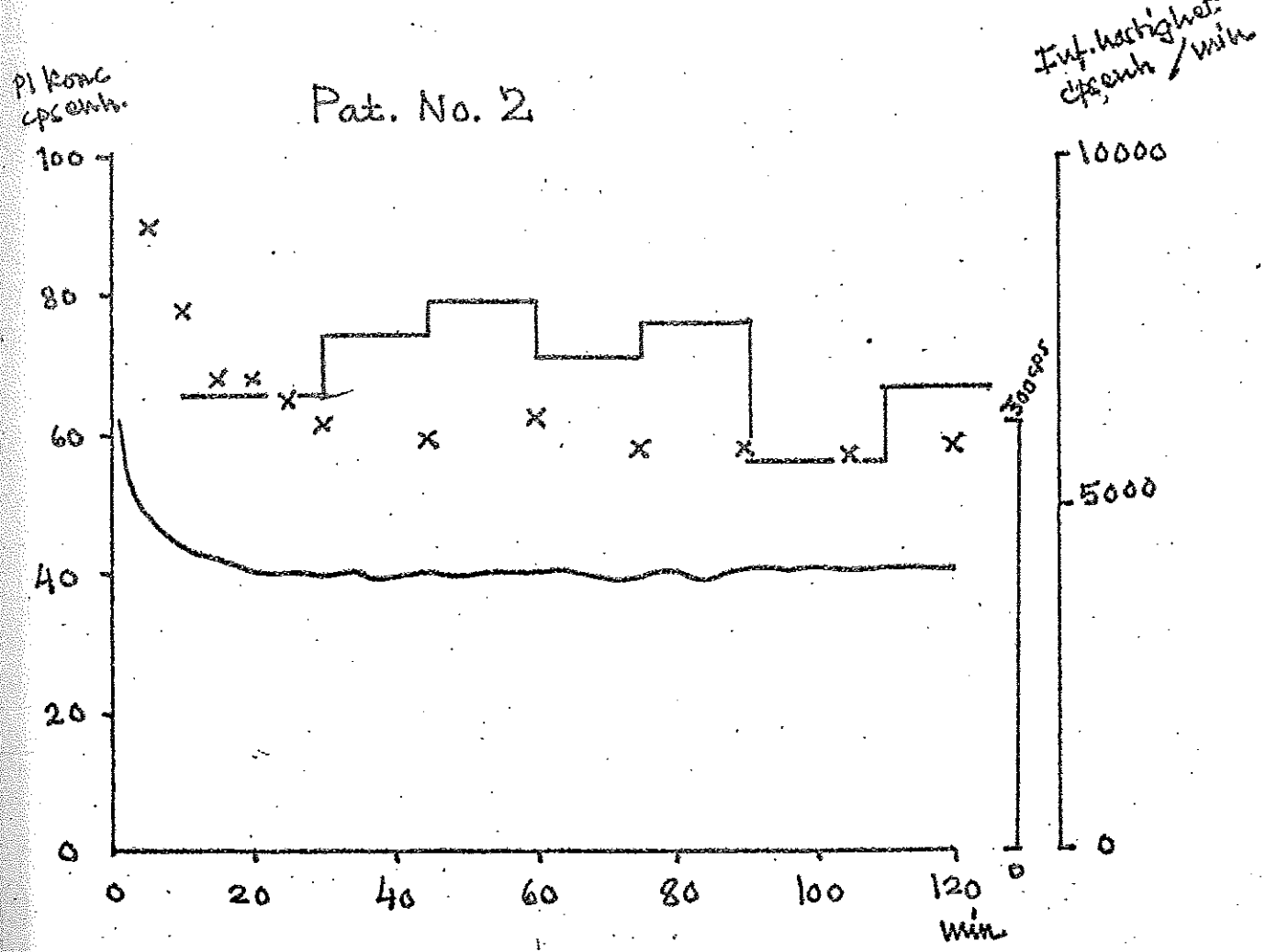
fig 2. Tracer distribution model

SYMBOLS: x x Plasma concentration

Precordial count rate (Ext. det.)

Infusion rate

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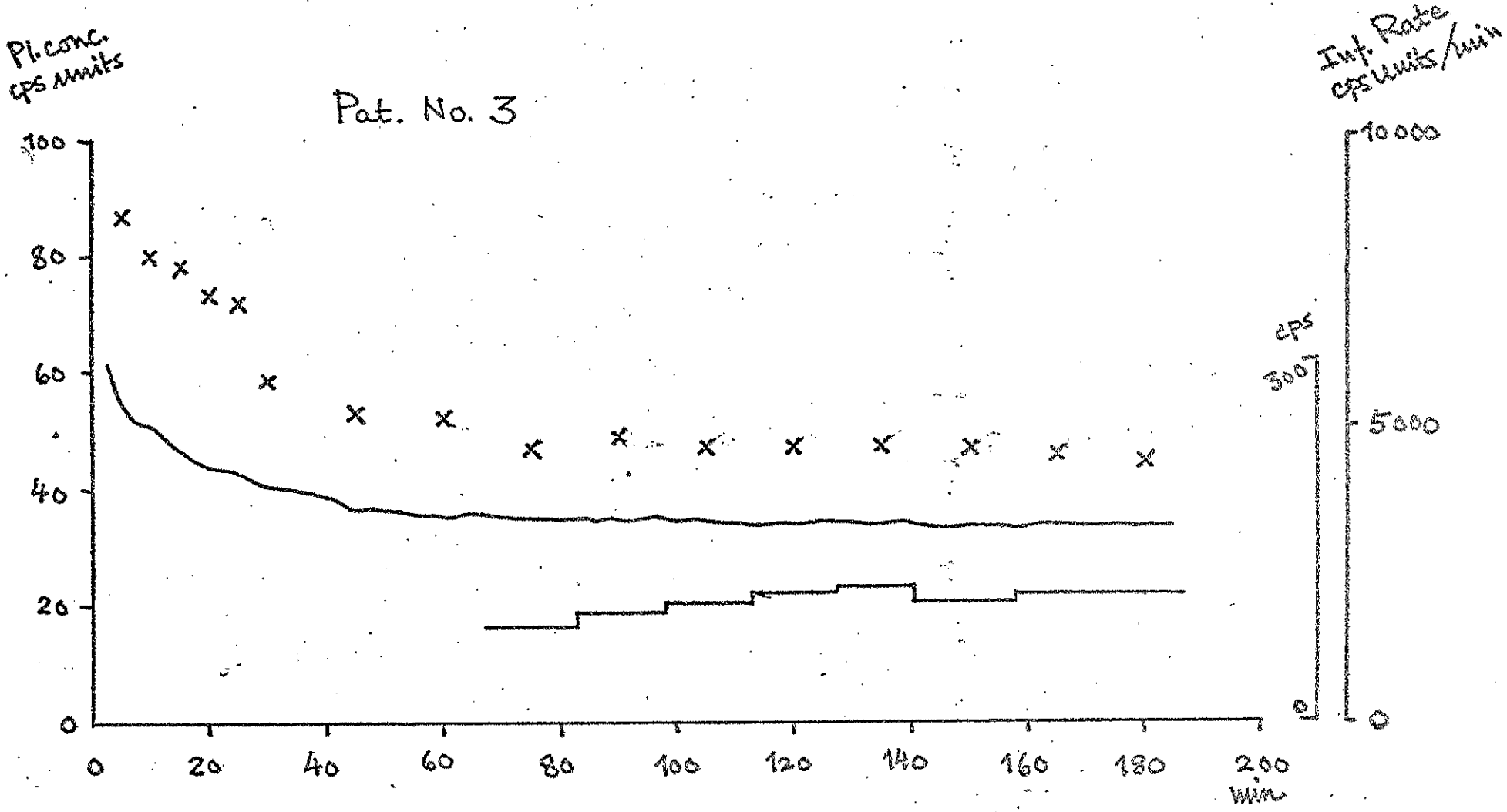
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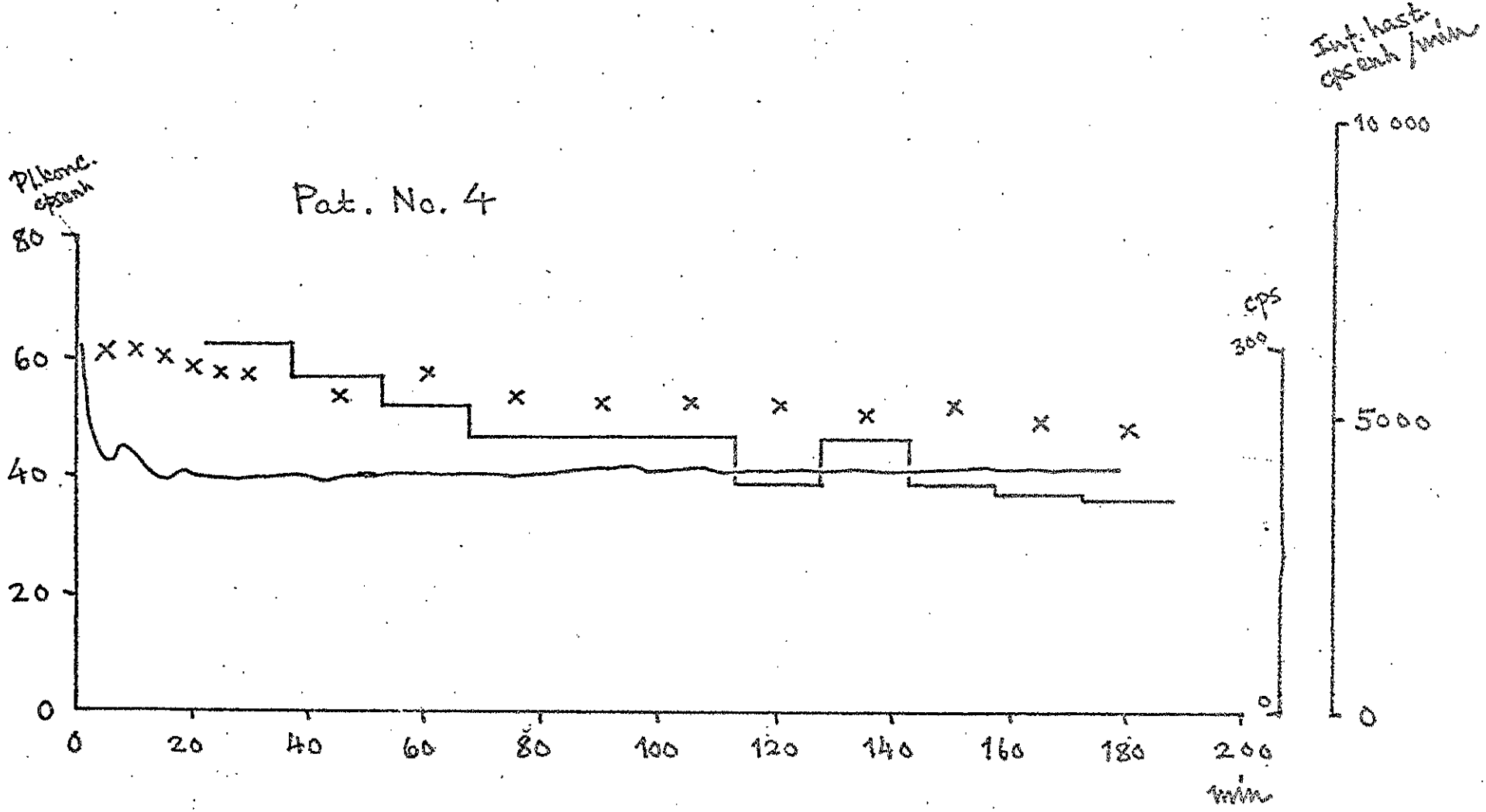
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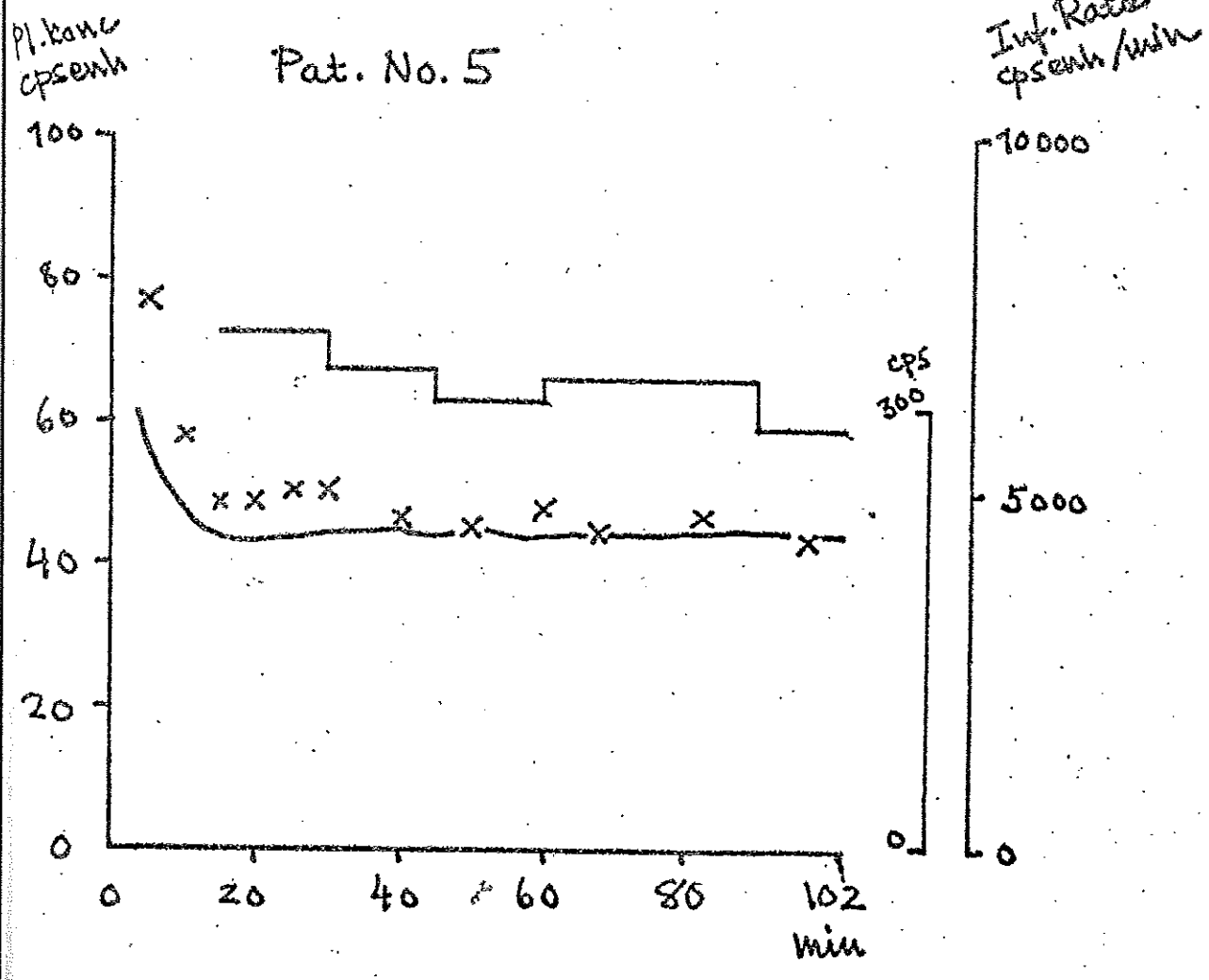
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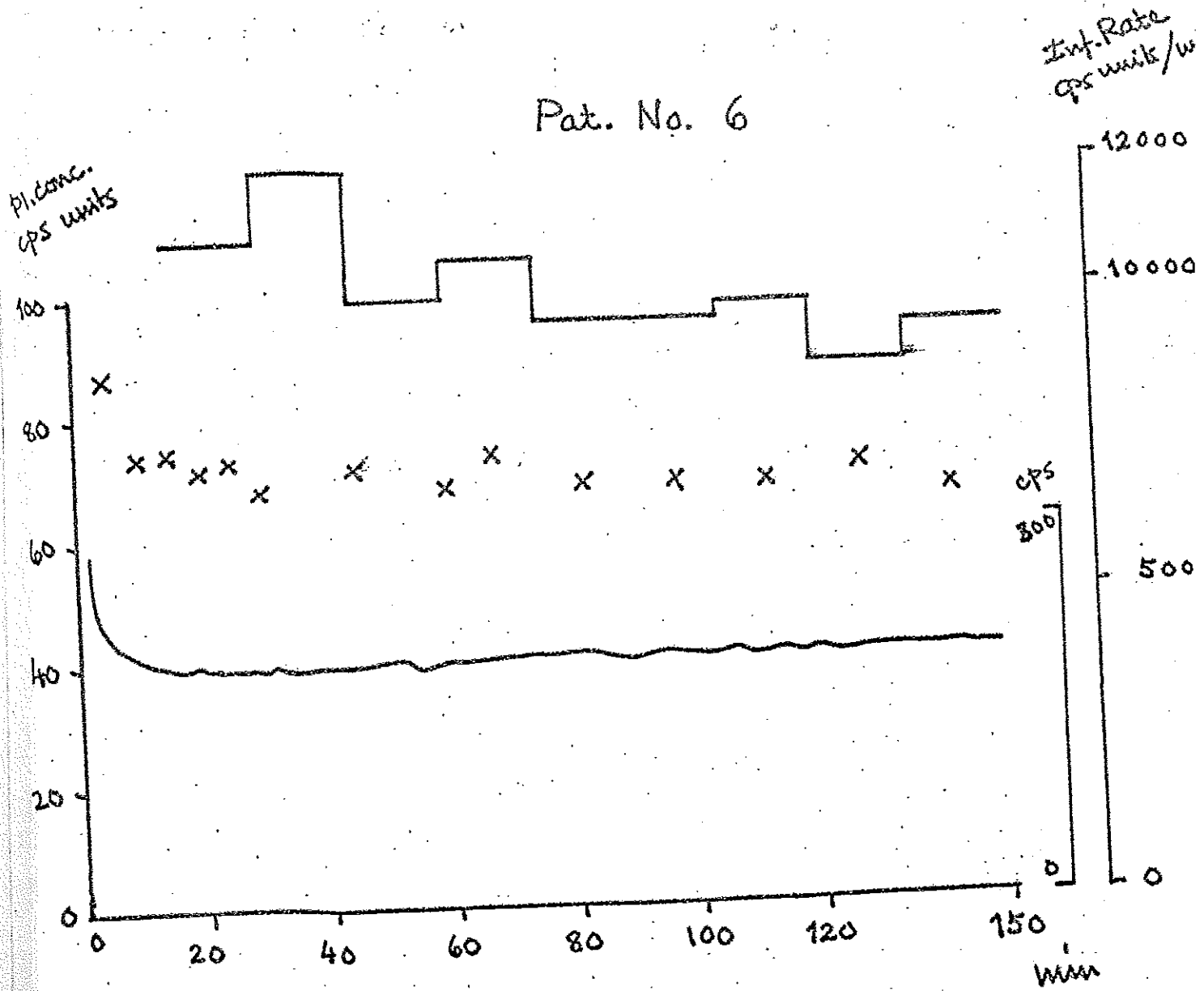
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