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EXTRACORPOREAL IRRADIATION OF BLOOD: MATHEMATICAL CONSIDERATIONS OF THE RADIATION DOSE DELIVERED TO A LIQUID BEING PUMPED THROUGH A RADIATION FIELD FROM AND BACK TO A RESERVOIR.*

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We have reasoned that the diversion of a portion of the blood flow through an extracorporeal shunt in an irradiation field would be helpful in the study of:

a. Radiation response of circulating elements in the peripheral blood.

b. Radiation injury of circulating plasma proteins.

c. Kinetics of blood cell production (particularly the lymphocyte family).

d. Therapy of selected leukemias in animals and man.

e. Cardiac output and flow through selected organs by radioisotopic techniques.

Our first paper demonstrated the induction of a lymphopenia by irradiation of the blood in an extracorporeal field (1). The second paper described a heparin lymphocytosis and its mechanism of production (2). The third paper describes the pumping technique in detail (3) and this paper considers the radiation dosimetry of partial extracorporeal circulation of blood through a radiation field.

EXPERIMENTAL DESIGN:

Details of the experimental set up have been published (1,3). For orientation, a schematic diagram and photographs of the experimental set up are presented in Figure 1.

The flow rate through the shunt is 300 ml per minute. The dose rate is approximately 300 r per minute. The transit time through the irradiation field is about 3 minutes.

Nomenclature:

R - total cardiac output

V - blood volume of animal i.e. internal circulation volume.

"transit" - is the unit of time. This is the time taken for a cell to traverse the external circuit.

r - volume of external circuit.

This is also numerically equivalent to the rate of flow through the external circuit because of the choice of unit time defined above.

n cells - these are the cells in the internal circuit that have traversed the external circuit n times.

In the following two considerations of the problem, it is assumed that:-

a) There is no longitudinal interchange of cells in the external circuit. This is equivalent to postulating that the cells leaving the external circuit at time t transits are the same ones that entered at time t-1 transits.

b) There is instantaneous and uniform mixing in the body. That is to say that a particular cell having traversed the external circuit and having just reentered the body has an equal probability immediately thereafter of reentering the external circuit.

The work of Nylin and Celander (4) describes a method for the determination of the "General Dilution Curve", D(t), for erythrocytes in the pulmonic portion of the total circulation. Its relationship to the circulation time distribution function is shown by the following considerations.

$I(t)\Delta t$ is the fraction of cells having circulation time between t and $t+\Delta t$. It is, then, the ratio of the number of tagged cells passing the observation point on their first circuit between t and $t+\Delta t$ to the total number of tagged cells passing the observation point on their first circuit. Mathematically, this is expressed by

$$I(t)\Delta t = \frac{D(t)\Delta t}{\int_{t=0}^{\infty} D(t)\,dt}$$

I(t) and D(t) differ only by a normalization factor that makes

$$\int_{t=0}^{\infty} I(t)dt \quad \text{equal to unity}$$

Consideration I

I(t) - is the circulation time distribution function from right ventricle to right ventricle avoiding the external circuit.

$I(t)\Delta t$ - is the fraction of cells having a circulation time between t and $t+\Delta t$.

J(t) - is the circulation time distribution function from external circuit to external circuit.

N - is the total number of cells per unit volume in the right ventricle.

$F_n(t)$ - is the fraction of n-cells in the right ventricle at time t.

The total number of n-cells leaving the right ventricle per unit time at time t is $F_n(t) \cdot N \cdot R \cdot$ ----- (1)

Of these, the number that originated in the right ventricle between time $t-P$ and $t-(P+\Delta P)$ and did not pass through the external circuit is

$$F_n(t-P) \cdot (R-r) \cdot N \cdot I(P)\Delta P \cdot \quad \text{----- (2)}$$

Note that $I(P)\Delta P$ by definition of the circulation time distribution function is the fraction of cells having circulation time (from right ventricle to right ventricle, avoiding the external circuit) between times P and $P+\Delta P$.

Similarly the number of these cells that originated in the right ventricle between time t-Q and $t-(Q+\Delta Q)$ and did pass through the external circuit is

$$F_n(t-Q) \cdot r \cdot N \cdot J(Q)\Delta Q \qquad \text{------} \quad (3)$$

$$\therefore \quad F_n(t) \cdot N \cdot R = \int_{P=0}^{\infty} F_n(t-P) \cdot (R-r) \cdot N \cdot I(P)dP \cdot +$$

$$\int_{Q=1}^{\infty} F_{n-1}(t-Q) \cdot r \cdot N \cdot J(Q)dQ$$

For mathematical convenience, substitute $Q = Z + 1$

$$F_n(t) \cdot = \frac{R-r}{R} \int_{P=0}^{\infty} F_n(t-P)I(P)dP +$$

$$\frac{r}{R} \int_{Z=0}^{\infty} F_{n-1}(t-1-Z)J(Z+1)dZ \qquad \text{- - - - -} \quad (4)$$

The first order Taylor approximations are:-

$$F_n(t-P) = F_n(t)-P \cdot \frac{d}{dt}[F_n(t)] \qquad \text{- - - - -} \quad (5)$$

$$F_{n-1}(t-1-Z) = F_{n-1}(t-1)-Z \frac{d}{dt}[F_{n-1}(t-1]$$

Whence noting that:-

$$\int_{P=0}^{\infty} I(P)dP = 1 \qquad \text{- - - - - (6)}$$

$$\int_{Z=0}^{\infty} J(Z+1)dZ = 1$$

Then from (4), (5) and (6)

$$\frac{d}{dt} F_n(t) + n F_n(t) = m F_{n-1}(t-1) - mb \frac{d}{dt} \left\{F_{n-1}(t-1)\right\} \qquad \text{- - - - - (7)}$$

where $m = \frac{r}{i(R-r)}$

$$b = \int_{Z=0}^{\infty} Z \cdot J(Z+1)d Z$$

and $$i = \int_{P=0}^{\infty} P \cdot I(P)d P$$

The exceptional equation becomes

$$\frac{d}{dt} F_o(t) + m F_o(t) = 0 \qquad \text{- - - - - (8)}$$

The boundary values are:

$$F_o(0) = 1 \qquad \text{- - - - - (9)}$$

and $$F_n(n) = 0 \qquad \text{- - - - - (10)}$$

The solution of (8) is

$$F_o(t) = \exp(-mt) \qquad \text{- - - - - (11)}$$

$$F_n(t) = \left[\frac{A^n(t-n)^n}{n!} - \frac{(n-1)m\ b\ A^{n-1}(t-n)^{n-1}}{(n-1)!} \right] \exp\left[-m(t-n) \right]$$

- - - - - (12)

Where $A = m + m^2b$.

The proof of (12) by induction follows. Note that it holds for $n = 1$. Assume that it holds for $F_{n-1}(t)$. The subsequent proof of its validity of $F_n(t)$ implies its validity for all n.

Let $F_n(t)=G_n(S)$ where $S=t-n$. Substitution into the right side of 7, ignoring lower order terms, leads directly to the expression

$$(j\ S^{n-1} - K\ S^{n-2})\exp(-ms) \qquad \text{- - - - -} \qquad (13)$$

where $$J = \frac{A^{n-1}}{(n-1)!}\ (m+m^2b) \qquad \text{- - - - -} \qquad (14)$$

and $$k = \frac{(n-2)}{(n-2)!} \cdot A^{n-2} \cdot m^2b + \frac{(n-1)}{(n-1)!} \cdot A^{n-1} \cdot mb + \frac{(n-2)}{(n-2)!} \cdot A^{n-2} \cdot m^3b^2$$

- - - - - (15)

Taking the Laplace transform of both sides of 7 and using the boundary value $G_n(0)=0$, one arrives at the identy

$$L\left[G_n(S) \right] = j\left[\frac{(n-1)!}{(p+m)^{n-1}} \right] - k\left[\frac{(n-2)!}{(p+m)^n} \right]$$

- - - - - (16)

whence

$$G_n(S) = \left[\frac{j}{n} \cdot S^n - \frac{k}{(n-1)} S^{n-1} \right] \exp(-mS)$$

- - - - - (17)

But $\frac{j}{n} = \frac{A^n}{n!}$ and $\frac{k}{(n-1)} = \frac{(n-1)mbA^{n-1}}{(n-1)!}$

Thus the expression for $F_n(t)$ in 12 is established for all integral n.

Consideration II

N is the total number of cells per unit volume in the circulation.

$F_n(t)$ is the fraction of cells in the internal circulation at time t that have passed through the external circulation n times.

Note that the flow rate is r units of volume per transit and therefore is Δt transits the flow is $\Delta t \cdot r$ units of volume.

The following changes will occur in the small interval of time Δt following any time t:

a) $F_n(t) \cdot N \cdot \Delta t \cdot r$ n-cells leave the animal's circulation and enter external circulation. Note that the flow rate is r units of volume per transit and therefore in Δt transits the flow is $\Delta t \cdot r$ units of volume.

b) $F_{n-1}(t-1) \cdot N \cdot \Delta t \cdot r$ n-cells enter the animal's circulation from the external circulation. These cells left the animal's circulation as (n-1)-cells one transit before they re-enter as n-cells.

c) The increase in the number of n-cells in the animal is $F_n(t+\Delta t) \cdot N \cdot V - F_n(t) \cdot N \cdot V$ Since the changes in c) may be attributed to the effects of a) and b), we obtain

$$F_n(t+\Delta t) \cdot N \cdot V - F_n(t) \cdot N \cdot V = F_{n-1}(t-1) \cdot N \cdot \Delta t \cdot r - F_n(t) \cdot N \cdot \Delta t \cdot r \qquad (18)$$

or $$\frac{F_n(t+\Delta t) - F_n(t)}{\Delta t} = \frac{r}{V} F_{n-1}(t-1) - F_n(t)$$

This is equivalent to the differential equation

$$\frac{dF_n(t)}{dt} + \frac{r}{V} F_n(t) = \frac{r}{V} F_{n-1}(t-1) \qquad n > 0 \qquad (19)$$

For n=0 one may derive the exceptional equation

$$\frac{dF_0(t)}{dt} + \frac{r}{V} F_0(t) = 0 \qquad (20)$$

Now $F_o(0)=1$ implies that

$$F_o(t) = \exp\left(\frac{-r}{V} \cdot t\right) \qquad \text{- - - - -} \quad (21)$$

By solving the differential equation for n=1,2,3.... successively and applying the boundary values $F_n(n-1)=0$ one obtains the general formula

$$F_n(t) = \frac{r^n}{V^n} \quad \frac{(t-n+1)^n}{n!}\left(\exp \frac{r}{V}(n-t)\right) \qquad \text{- - - - - -} \quad (22)$$

when $\frac{dF_n(t)}{dt} = 0$, then $F_n(t)$ has its maximum value.

Note that $F_n(t)$ has its maximum value at $t=T_n$

given by $T_n = n\frac{V}{r} + \left(n-1\right.$ - - - - - - - (23)

and its maximum value is

$$F_n(T_n) = \frac{n^n}{n!} \exp\left(\frac{r}{V} - n\right) \qquad \text{- - - - -} \quad (24)$$

Sample Calculation:

With the following factors:

Blood volume	14.0 liters (V)
External volume	0.9 " (r)
Transit time	3.0 minutes
Dose rate	300 rads/minute

One can compute the size of the largest fraction of the blood volume for any given dose to this largest fraction. For a dose of 8100 rads to this largest fraction the number of transits (n) will be 9. Then from equation (23) the

total number of transits can be computed.

$$T_n = \frac{n\,V}{r} + (n-1)$$

$$= \frac{9 \times 14}{0.9} + (9-1) = 148 \text{ (total transits).}$$

From equation (22) with the above conditions one can compute the fraction of the blood which has gone through the external circuit between the imposed limits of 0 and 148. The approximate numerical values are tabulated in Table 1 and converted into dose for values of n varying from 1 to 18.

SUMMARY:

1. In a system where liquids are being pumped from and back to a continuously mixing reservoir through a radiation field, a mathematical approach is presented that will answer the following questions:

a) With any constant flow rate and time of pumping through a radiation field of any constant intensity, the size and distribution of any fraction of the liquid receiving any radiation dose can be computed.

b) If the largest possible fraction of such a liquid is to receive a certain ionizing radiation dose; the flow rate and time of irradiation can be computed.

2. These dose considerations are essential for an understanding of radiation effects upon all types of blood cells and macromolecules flowing through the radiation field described.

3. This technique will allow a study of radiation injury of blood cells of all types and circulating plasma macromolecules without the complications imposed by radiation injury of the tissues since only the extracorporeal shunt is irradiated.

4. This technique and the mathematical analysis of the dose received in the shunt may be directly applicable to problems in pure radiation chemistry where equilibria between the non-irradiated reservoir and the irradiation shunt can be studied.

5. Although the mathematical principles of dose computation have been worked out in theory, the mechanical computation is so time consuming that programming on an appropriate digital computer is essential and has been accomplished with the Brookhaven National Laboratory Merlin.

Table 1. Dose Distribution for 7 Hours and 24 Minutes Irradiation.

n	$P_n(148)$	Dose $x10^2$	n	$P_n(148)$	Dose $x10^2$
1	0.001	9	11	0.106	99
2	0.004	18	12	0.076	108
3	0.013	27	13	0.050	117
4	0.032	36	14	0.030	126
5	0.062	45	15	0.017	135
6	0.097	54	16	0.008	144
7	0.130	63	17	0.004	153
8	0.139	72	18	0.001	162
9	0.140	81			
10	0.134	90			

Figure 1. Schematic diagram of experimental set up and photographs of actual arrangements.

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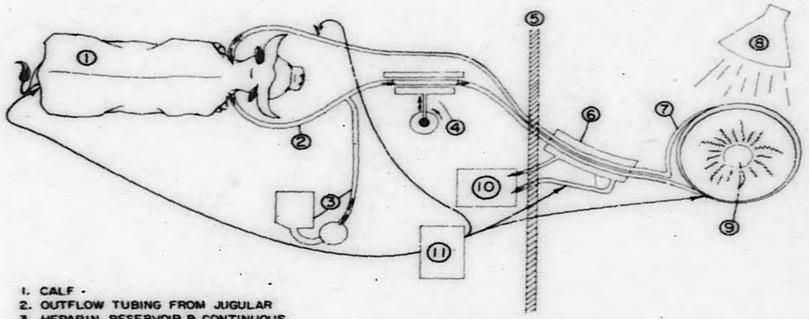
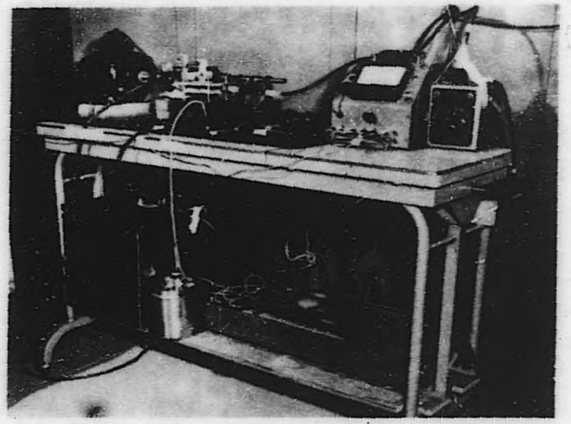
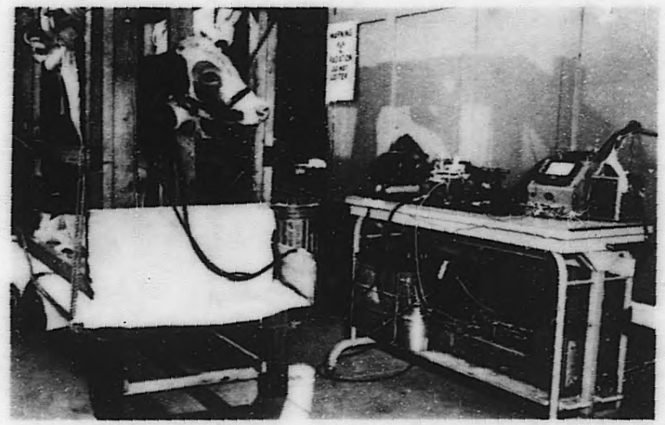
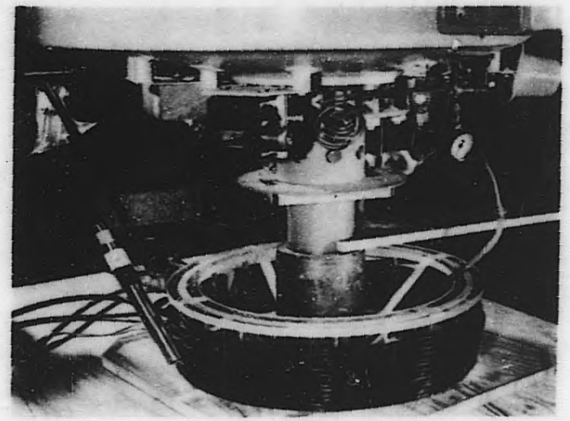


1. CALF -
2. OUTFLOW TUBING FROM JUGULAR
3. HEPARIN RESERVOIR & CONTINUOUS INFUSION PUMP
4. EXTRACORPOREAL PUMP
5. LEAD BARRIER
6. HEATING JACKET 40°C
7. IRRADIATION COIL (1100 ml VOLUME)
8. INFRA RED HEATING LAMP
9. 360° X-RAY MACHINE
10. WATER HEATING BATH & PUMP FOR HEATING JACKET
11. RECORDER FOR THERMISTORS AT WATER JACKET, RADIATION COIL, INFLOW TO ANIMAL & AT RECTUM







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