Cineradioangiographic Visualization of the Venous Drainage of the Primate Placenta in vivo

Abstract. *Radiopaque dye injected directly into the intervillous space of the placenta of the rhesus monkey may be observed, by cineradiography, as it spreads throughout the space and drains into the veins of the uterine wall and eventually into the systemic circulation.*

Radioangiographic studies in the rhesus monkey have established the manner in which maternal blood enters the intervillous space of the primate hemochorial placenta (*1*). A continuation of these studies, to be reported herewith, shows the manner in which blood leaves the intervillous space and drains into maternal veins.

Observations of placental drainage have been made at close intervals throughout pregnancy by the following method. In a monkey anesthetized with Nembutal, a polyethylene catheter is introduced into the amniotic cavity via a needle inserted through the intact abdominal wall. The catheter is connected with a strain gauge pressure transducer and direct writing polygraph to record myometrial activity as reflected in intrauterine pressure (*2*). When the record has stabilized, laparotomy is performed. The uterus is transilluminated to localize the two placental disks, and a No. 17 gauge needle is inserted into the intervillous space of the more accessible one. The needle is attached by a connecting catheter to a 10-ml syringe containing the radiopaque dye Renovist. The abdominal incision is closed temporarily with through and through sutures. When the changes in myometrial activity occasioned by the surgery have disappeared, 5 ml of the dye are injected by manual pressure as rapidly as possible. Injection requires 1 to 2 seconds because of the small caliber of the catheter and needle. Just before the start of the injection, cineradiography is commenced to permit visualization of the entry of the dye into the intervillous space and its progress into the uterine veins.

Continuous observation of the dye flow is achieved by means of televised amplified fluoroscopy viewed on one of two television monitors (*3*). Cineradiographic recordings of the entire examination or of certain parts of it are made directly from the output phosphor of the electron image intensifier at a rate of 30 frames per second. The kilovoltage is maintained at a level between 70 and 80. The milliamperage is automatically controlled according to the size of the subject. The milliamperage during fluoroscopy is approximately 0.5 and varies during the cinerecording between 1 and 2, pulsed grid x-rays being used.

As the dye emerges from the tip of the injecting needle it fans out into the intervillous space around, among, and in between the chorionic villi which crowd the space. The radiologic image of the course of the dye is that of a fine feather whose growing tips, in a matter of seconds, establish communication with the network of maternal veins in the endometrium by way of the numerous orifices distributed all over the basal plate of the placenta (*4*) (Fig. 1). A few seconds later the dye has passed further out into the uterine venous system and entered the short, wide, radial channels which connect the endometrial plexus with the arcuate veins of the myometrium. From these broad circumferential channels the dye passes into the uterine and ovarian veins and thence to the inferior vena cava and the systemic circulation (Fig. 2). It may be noted that the caliber of the intramural vessels markedly increases as pregnancy advances (Fig. 3).

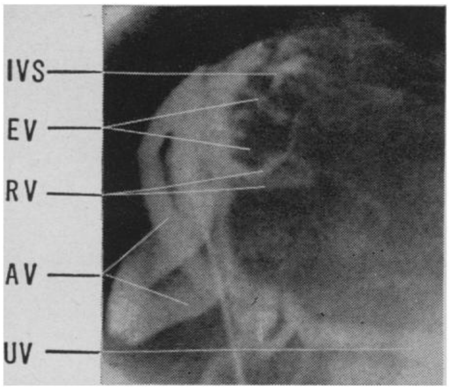
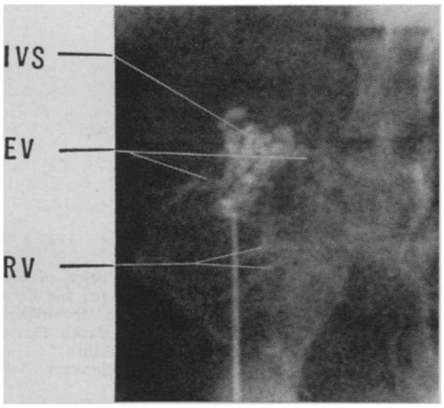


Fig. 3. Photograph of a radiogram made 9.5 seconds after injection of dye. Little dye remains in the intervillous space. The radial and myometrial veins are well filled with dye which has now entered the systemic circulation. Labels as before. Monkey 62-24; 139th day of pregnancy (enlarged from 16-mm film).



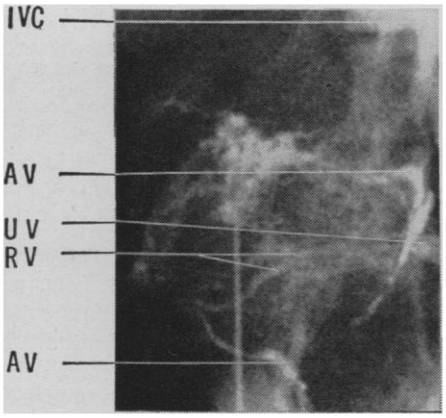


Fig. 1 (left). Photograph of a radiogram made 1.5 seconds after injection of radiopaque dye into the intervillous space. The feathery appearance of the dye at the needle's tip is the result of its course among the dense crowd of chorionic villi. *IVS*, intervillous space; *EV*, endometrial veins; *RV*, radial veins. Monkey 7B; 67th day of pregnancy. Fig. 2 (right). Photograph of a radiogram in monkey 7B, made 3.9 seconds later than that shown in Fig. 1. The dye has reached the radial and myometrial veins. Labels as in Fig. 1, plus: *AV*, arcuate veins; *UV*, uterine vein; *IVC*, inferior vena cava (enlarged from 16-mm film).

To date the only observed effect of myometrial contractions upon the course of drainage consists in a slight delay in the appearance of the dye in the veins of the uterine wall if it has been injected during a phase of strong myometrial contraction. The matter is currently the object of closer investigation.

The present report provides the first cineradiographic demonstration of the configuration of the intervillous space of the primate placenta in vivo and of the pathways of drainage of blood from the intervillous space all the way to the systemic circulation (*5*).

ELIZABETH M. RAMSEY
Department of Embryology,
Carnegie Institution of Washington,
Baltimore 10, Maryland
GEORGE W. CORNER, JR.
MARTIN W. DONNER
Departments of Gynecology and
Obstetrics and *Radiology, Johns*
Hopkins University and *Hospital,*
Baltimore, Maryland

References and Notes

1. E. M. Ramsey, G. W. Corner, Jr., M. W. Donner, H. M. Stran, *Proc. Natl. Acad. Sci. U.S.* **46**, 1003 (1960); E. M. Ramsey, G. W. Corner, Jr., M. W. Donner, *Am. J. Obstet. Gynecol.* **86**, 213 (1963).
2. E. M. Ramsey, G. W. Corner, Jr., W. N. Long, H. M. Stran, *ibid.* **77**, 1016 (1959); G. W. Corner, Jr., E. M. Ramsey, H. M. Stran, *ibid.* **85**, 179 (1963).
3. M. W. Donner, E. M. Ramsey, G. W. Corner, Jr., *Am. J. Roentgenol. Radium Therapy Nucl. Med.*, in press.
4. E. M. Ramsey, *Am. J. Anat.* **98**, 159 (1956).
5. Supported in part by research grants (3B-9040 and AM 04676-02) from the U.S. Public Health Service and from the Upjohn Company.

27 May 1963

Redundancy and Biological Aging

Abstract. *The relationship between aging and organizational redundancy in biological systems was investigated from the standpoint of information theory. A mortality rate function derived for a randomly deteriorating redundant system approximates observed mortality rates more closely than does the Gompertz function and indicates that variations in redundancy among various mammalian species could account for their widely different rates of aging.*

From the standpoint of information theory, all organization in a system can be lumped together and quantified as information. With the passage of time, in any living system there is a progressive loss of organization and an irreversible accumulation of informational entropy. Some degree of compensation for this process can be afforded by the incorporation of redundant information, or spare parts, so to speak, into the system, a principle analogous to the use of redundancy in messages carried over noisy communications channels, or the use of parallel systems to improve reliability of control systems. That such protective adaptation would have a positive survival value and might therefore be of fundamental importance in living systems was pointed out by Dancoff and Quastler (*1*) over 10 years ago.

Detailed application of this abstract notion to a living organism is a complex problem, since essential information, redundant in part, is manifest at all organizational levels from molecular structure to gross anatomy. The importance of redundancy at the organ level is well known. Over 75 percent of mammalian renal tissue, for example, seems to be redundant, since over three-fourths of the kidney tissue of a healthy mammal must be removed to produce renal failure. Much has been written on the information content of macromolecules (*2*), and Ehret (*3*) has estimated the information requirement at the cell organelle level, but just what part of this information is redundant is not known.

It is much easier, though less descriptive, to consider the pooled information from all levels of organization. Effective pooled redundancy can be estimated to some extent by measuring the reserve capacity of a complex function requiring intact information at many levels. The studies by Shock and collaborators (*4*) of basal metabolic rate, work rate, cardiac output, pulmonary function, nerve conduction velocity, and renal function have shown that losses of 20 to 60 percent of function during aging are still compatible with life, indicating overall redundancies of at least 20 to 60 percent for these complex functions.

In this investigation of the effect of redundancy upon aging, biological age will be expressed as the probability, at time t, of death within a given time interval. This probability, equivalent to the age specific mortality rate or the q_x of actuarial tables, can be written

$$-\frac{1}{S}\frac{dS}{dt} \equiv -\frac{S'}{S} = f(t)$$

where S is the number of survivors at time t. Throughout the last two-thirds of life this is generally considered to be a simple exponential function as originally proposed by Gompertz (*5*). In most mortality studies, however, the rise of $-S'/S$ is somewhat less than exponential. This has been emphasized by Strehler (*6*) in the case of *Drosophila*, by Lindop (*7*) in the case of mice, and by Auerbach (*8*) in the case of human mortality statistics.

Considering the living organism as a collection of information, the present problem is to examine the mortality rate curve (S'/S versus t) of a randomly decaying ensemble of message-laden, redundant information.

A large part of the total information of an organism is expendable, being either unnecessary or readily replaced. There is, however, a body of information which is replaced with difficulty or not at all. Errors which accumulate here are perpetuated throughout the life of the individual. This vital information is held to some degree in larger structures but chiefly in certain irreplaceable cells of nonproliferating cell populations and in the progenitive cells of renewal cell populations. Within these cells the main repository of information is in the structure of nucleic acids, by which all protein synthesis is directed.

A certain minimum of this vital information is necessary for life. This minimal or essential message is carried in a minimal ensemble of structural elements, ω in number, which will be assumed in the following model to be largely independent. Since various types of structural units carry various amounts of information, it will be necessary to use a mean value of b bits of information per structural element. The informational unit of the nucleic acids, the nucleotide pair, carries two bits of information, so that the overall mean of information per structural unit throughout the entire organism should be of this order. The essential message is then equal to $b\omega$ bits.

The repetition of structure throughout the organism gives redundancy to the complement of irreplaceable information. Since the variation of redundancy among various parts of the essential message is unknown, the simplest case, that in which redundancy of all elements is the same, will be used as a model. Redundancy is customarily given as a percentage, but it will be convenient here to define a redundancy number, n, such that

$$\%\ \text{redundancy} = 100\,(1 - 1/n)$$

where n is the number of times an informational structural element appears within the organism at the time of maximal redundancy. This is analogous to the "hitness" number in target theory. If $b\omega$ bits of information carry the essential message, then the full complement of information is

$$H_{\max} = nb\omega$$

This can be conveniently represented as a matrix of ωn elements:

$$\begin{array}{lcr}
A_1\ A_2\ A_3 & \ldots\ldots\ldots\ldots\ldots & A_n \\
B_1\ B_2\ B_3 & \ldots\ldots\ldots\ldots\ldots & B_n \\
C_1\ C_2\ C_3 & \ldots\ldots\ldots\ldots\ldots & C_n \\
\cdot & & \cdot \\
\cdot & & \cdot \\
\omega_1\ \omega_2\ \omega_3 & \ldots\ldots\ldots\ldots\ldots & \omega_n
\end{array}$$

Each element is an independent, structural unit carrying b bits of information; all members of class A carry identical pieces of information; and the essential message reads downward from any A to any ω. At least one element of each class must be present to retain the essential message.

Now let structural elements decay with time in the manner of a first-order chemical reaction. Errors will accumulate in the matrix in a random fashion. If the mean probability of an