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A PROPOSAL

FOR

DEVELOPMENT AND USE OF

METHODS FOR MEASURING

BLOOD FLOW RATES IN TUMORS

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Measurement of Blood Flow Rates in Tumors

I. INTRODUCTION

A knowledge of the blood flow rates in tumors and of the effects of various pharmacological and physiological factors on these flow rates has potential applications in many aspects of the diagnosis and treatment of tumors. In particular, the detectability of tumors by radioisotopic methods is in part determined by the differences in blood flow rates for the tumors and those for adjacent normal tissues. In therapy, the blood flow affects the oxygenation of tumors, which in turn affects their relative sensitivity to radiation therapy. (With low LET radiations, such as x-rays and ^{60}Co gamma rays, a reduction of oxygen tension tends to reduce the sensitivity of tissues to the radiation, whereas an increased oxygen tension increases the sensitivity to radiation.) Similarly, the effectiveness of chemotherapy may be influenced by blood flow rates because critical concentrations of the active agents cannot be attained and sustained without adequate delivery rates of these agents to the sites of action.

Important as the blood flow rates of tumors may be, a survey of the literature reveals that this subject has received less attention than may be expected. As will be brought out in the following exposition, there are many factors which have served to discourage attempts to obtain the desired data, including inherent difficulties and the cost of the required equipment. It is proposed, however, that studies be undertaken to develop the necessary techniques and to begin to obtain the desired data.

II. PROPOSED STUDIES (general aims)

It is proposed that studies be initiated with the following objectives:

(1) To determine the feasibility of making quantitative measurements of blood flow rates in tumors in human patients.

In this phase of the study measurements will actually be made largely on animals and phantoms, but using methods which would be acceptable for use with human patients. Animal and phantom studies are necessary for establishing the accuracy and precision of indirect methods through comparison with the results of direct methods.

(2) If the above studies affirm the feasibility, to proceed with obtaining such measurements in a variety of types and locations of tumors in human patients.

It is expected that this phase of the studies would involve having patients under study or treatment at other institutions in the area referred for one or more relatively short admissions to the BNL Hospital for the proposed studies. The studies conducted at BNL would be restricted to obtaining the necessary documentation regarding the type and location of the tumor(s) and to applying the indicated diagnostic and/or research procedures. Actual treatment of the tumors by surgery, radiation or chemotherapy would not be undertaken under this proposal.

(3) To develop additional instrumentation or modifications of existing equipment as may be necessary to achieve the first two objectives. This phase will also require some theoretical considerations for interpretation of the data and for optimizing the equipment under development.

III. LITERATURE ON REGIONAL BLOOD FLOW MEASUREMENTS

The physiological literature on regional blood flow prior to 1965 is thoroughly reviewed from a number of different view points in several chapters of section 2: Circulation, of the Handbook of Physiology (1). Later reviews by Greenfield (2), Spencer (3), Rovick and Randall (4) Sonnenschein and White (5), and Ross (6) provide scores of references to studies of blood flow rates in various organs and tissues. Among the organs which have received most intensive attention in blood flow studies are the brain, the liver, the heart, the lungs, the kidneys, bone, the hand and arm, the stomach, muscle, the intestine, the pancreas, and the spleen. Attempts have also been made to measure blood flow rates in glands and other smaller structures with varying degrees of success.

In general, the physiological literature cited is concerned with measurements of blood flow rates in normal organs of the body or those with circulatory defects, and not with blood flow rates in tumors. It does, however, provide information on a wide range of methods, some of which may be brought to bear on the latter problems.

The first article primarily concerned with absolute determinations of the blood flow to tumors appears to have been that published by Gullino and Grantham (7). These authors used a direct method, involving collecting venous blood from transplanted, tissue-isolated tumors, and an indirect method based on the uptake of ^{42}K Cl or ^{86}Rb Cl in the tumors of animals killed at various times after injection of the tracer into the femoral vein. They found that transplanted tumors in the species studied tended to have lower blood flow rates than did the tissues of origin. These findings were supported by Cataland et al. (8), who also found an inverse relationship between tumor size and tumor blood flow rates expressed as percent of cardiac output per gram. It was clearly recognized that the results obtained with transplanted tumors do not necessarily apply to tumors of spontaneous origin. However, Arnold (9) using ^{99m}Tc and an Anger camera technique for uptake rates with human patients found that primary hepatomas, meningiomas, hemangiomas, renal cell carcinomas, and, to a lesser extent, gliomas, have larger blood flow rates than the organ parenchyma, but metastatic carcinomas were found to be generally less well perfused than surrounding parenchyma. These studies involved only relative rates of uptake of the tracer used and could not be made quantitative. In general the benign tumors show an increased relative blood flow but the malignant ones do not. This could be due in part to the presence of necrotic areas in the latter types.

Certain other aspects of the blood flow to tumors such as the relative effects of various drugs, inhalation of CO_2, etc., are found in a number of scattered papers (10-26). Although some pertinent papers may well have been missed in this survey of the literature, it seems clear that the literature available on studies in the area of interest is not extensive, and that hardly any quantitative data have been reported.

IV. LITERATURE ON METHODS

There is no shortage of methods that have been used for measuring regional blood flow rates. Here again the Handbook of Physiology (1) provides numerous references to the pre-1965 literature. The chapters by Kramer, Lochner and Welterer (27) and by Spencer and Denison (28) are particularly directed to this topic, but there are many citations in other chapters as well. The latter chapter emphasizes the use of an electromagnetic flowmeter. The chapter by Kramer et al. provides a more general survey. As these authors point out, "Principles of measurement (of blood flow) may be and have been developed from almost every topic in physics textbooks: mechanics (solid, liquid and gas), sound, electricity, magnetism, optics, thermodynamics, and atomic physics."

More specifically, some methods or devices that have been successfully used include venous outflow collections, drop recording (for less than 2 ml/minute), bubble flowmeter, pulse plethysmography, photoelectric plethysmography, thermal stomuhr, thermal conductance methods (heat flow and temperature gradient in skin) and thermal conductivity (similar to preceding, but involves a special heat source). Another general reference is the chapter by Donato, Holmes and Wagner (29) in Wagner's book. Here, of course, the emphasis is on the use of radioactive indicator techniques. These methods have been applied in human beings for measuring cardiac output and blood flow rates to the brain, the myocardium, the kidneys, and the extremities. A recent article by Milder et al (30) describes the use of Indium-113m-iron hydroxide particles to measure blood flow in the dog lung.

V. APPLICATIONS IN TUMORS

When we come to the problem of measuring blood flow rates in tumors in human beings, few of the methods mentioned above are really useable. Some require hazardous surgical procedures, some are appropriate only for experimental animals because of involving transplanted tumors, killing the animals, destructive surgery or other unacceptable procedures. Others give, at best, relative values, which are of use in determining the direction of effects of a drug or procedure but which do not give quantitative results. The radioactive indicator methods that utilize external detection methods are the most acceptable from the viewpoint of the patient. These methods, however, have not enjoyed widespread utilization because of the complexity and cost of the required equipment. In particular there have been few studies which provide data on the blood flow rates in tumors.

VI. EQUIPMENT AVAILABLE

The following paragraphs describe some of the major items of equipment which are mentioned below under the proposed studies and which are currently in use at the BNL Medical Research Center or which are on order.

1. Nuclear Chicago Pho-Gamma III (Anger Camera). This is a commercially available device using a single large crystal and electronic circuitory designed to reconstruct and display a picture of the distribution of radioactivity in its field of view.

2. Multicrystal positron detector. This is a 32 crystal device developed at BNL (31) for locating brain tumors and currently in use for studies of cerebral blood flow. In the present configuration the 32 one-inch diameter NaI crystals are arranged in a circle of 40 cm diameter. Through the use of electronic coincidence circuits the counts due to positron annihilation gamma rays are recorded according to counter pairs. There is no collimation involved, and each crystal may be paired with any of the other crystals, thus providing a relatively high quantum utilization for the system. Through computer analysis of the data a tomograph, or mapping of the activity in the "plane" (actually a slab about 1 inch thick) of the crystals is produced.

3. Nuclear Data 50/50 Med System, with PDP-8 computer. This commercially available system provides automatic recording of data obtained with the Anger Camera or other detection devices and has the capability for achieving some data processing.

4. Ohio Nuclear Scanner

5. Fifty-four crystal (6 inch diameter NaI) whole body counter.

6. Cyclotron

A 60" cyclotron is available for the production of a wide range of short lived radioisotopes. It can accelerate protons, deuterons, alpha particles or helium-3 nuclei at energies of 2-20 MeV for deuterons to 6-60 MeV for the helium 3 nuclei. Beam currents up to 100 μa are available. The cost of the use of this machine is based on an hourly charge derived from the total operating cost of the machine. At present this is $84 an hour.

7. Computers

A XDS Sigma 2 computer with 32 K of core memory, two magnetic tape transports, a disc file, a card reader, a paper tape reader and a fast printer is located in the BNL Medical Research Center. This computer is connected via a special cable system, Brooknet, to the CDC 6600 computers located at the BNL central computer facility, thus providing direct access to a very powerful computer system. The Sigma 2 is also connected on-line with the multicrystal positron detector device and to the whole body counter.

VII. PROPOSED STUDIES (SPECIFIC METHODS)

The following paragraphs outline several techniques which will be used in studying the blood flow rates in tumors and which involve equipment currently available at the Medical Research Center of the Brookhaven National Laboratory. Some modifications of and additions to the present equipment may be necessary to meet the special requirements of the proposed studies.

For the present discussion, it will be assumed that from roentgenography and other diagnostic methods the location of the tumor to be studied is already known with some precision. Even so, the problem of measuring blood flow by external counting methods is a difficult one, particularly when the tumor is deep in the body and/or when it has a relatively low blood perfusion rate, by which is meant the blood flow per unit weight of the tumor.

In measuring blood flow, it is even more important than in related procedures used for locating tumors to eliminate the effects of radioactivity in the tissues between the tumor and the detector. Our 32 detector positron device provides one method for solving this part of the problem. Another method under consideration is to use focusing collimators on two Anger cameras placed on opposite sides of the body and to use a nuclide that emits two gamma rays of suitable energy. The combination of focusing collimators, coincidence counting, and data processing by computer methods permit one to "see through" overlaying activity and to determine the activity at the site of interest even if it is less than the overlying activity.

The theoretical basis for the latter method has been developed by Dr. H. Hart (City College of New York). Its translation into hardware and use would involve collaboration with Dr. Hart. These devices and others mentioned below would be used in the following procedures:

(a) Plasma volume and red-cell volume. Standard methods using ^{125}I radioiodinated serum albumin for plasma volumes and ^{51}Cr-sodium chromate labeled red cells are available for these determinations (30). With a correction for the white cell volume, the sum of these two volumes gives the total blood volume. Blood samples are counted in well counters for these determinations.

(b) Transit-time measurements. Transit-time measurements are best done following intra-arterial injection of tracer, but some information can be obtained following intravenous injections, particularly when a small bolus can be rapidly injected. A non-diffusible tracer should be used. The patients own labeled red blood cells would be ideal for this purpose. Two appropriate labels are available, ^{99m}Tc in reduced form (32) and ^{11}CO (33). The latter may be preferable when multiple studies must be performed in rapid succession. The labeling techniques are described in the references cited.

Various instruments can be used for this determination. Anger Camera interfaced with the Nuclear Data 50/50 Med System can be used in the dynamic mode for selection of the region to be studied and obtaining the necessary data in appropriate time intervals. The positron camera attachment to the Anger Camera is not suitable for dynamic studies, but the 32 detector positron device would be useful for this purpose.

Using the Anger camera-Nuclear Data system a typical plan would be as follows. A bolus of ^{99m}Tc sulfur colloid would be injected intravenously and the tumor and surrounding tissue visualized by display on the CRT. A continuous recording on magnetic tape of the data for these areas would make the data available for subsequent analysis. This would be followed by an intravenous injection of ^{11}CO labeled red cells for the flow measurements, again with continuous recording of the data. On replay, the region of interest as indicated by the first tracer and an adjacent control area would be defined by drawing their boundaries with a light pen. The time course of the second activity in these areas provides the data needed for computing the transit times. The accuracy of this method would be improved through the use of two opposing cameras.

(c) Blood volume within the tumor

This measurement could be achieved as a continuation of the transit-time measurements, with the recording proceeding until equilibrium is atained. By comparison with a count made with a tissue equivalent phantom, the fraction of the injected activity which appears in the tumor volume would be determined. From a blood sample the fraction of activity per ml of blood would be determined, and from the ratio of these two fractions the volume of blood in the tumor volume would be calculated. Again the anger camera-Nuclear Data system would be used for data acquisition and data processing.

(d) Blood flow rates

The tumor blood volume and the transit time determinations described above provide the information necessary for computing blood flow rates in absolute units such as ml/min. If BV = blood volume in the tumor and TT = average transit time for blood to flow through the tumor, the blood flow rate, BFR = BV / TT. The precision ascribable to this result depends on several factors, particularly the errors associated with the various counting rates involved. As a first approximation the standard deviation for a given total count is the square root of the count. Thus to achieve a low counting error it is necessary to have a large total count. In the proposed work there are limitations which preclude the achievement of arbitrarily low counting errors. The radiation dose to the patient must be kept within the established limits, which means that the amount of activity administered is limited. Even without this limitation, the limitations imposed by the instrumentation and by the requirement for short counting times in the dynamic studies militate to give relatively low total counts and consequent relatively large counting errors. When several parameters involving these errors are combined, the errors are also combined additively. It is expected that it will be difficult to obtain errors of less than 5 to 10 per cent in BV and TT, so the error in the blood flow rate by this method may be expected to be 10 to 20 per cent.

(e) Clearance rates. The use of an inert gas for measurement of washout rates has been used to measure blood flow in a number of tissues. For measurement of tumors in patients the gas would be inhaled until the tissues are saturated. Then the washout rate could be determined with the gamma camera. If a positron emitter (^{79}Kr) is used the 32 detector positron device would be suitable for measurement. The advantage of this system is the 3-dimensional localization of the region to be studied. Alternatively ^{13}N may be considered for these studies. Nitrogen has the advantage of having a lower binding coefficient for fatty tissues than does krypton, and thus the wash out time from the body would be shorter.

These method gives results expressed as perfusion rates, for example in units of ml/min. per 100 gm.

It is proposed that investigations be undertaken to explore the feasibility of applying the techniques mentioned above in the quantitative measurement of the blood flow rates of tumors in human beings, and to develop modifications of these methods or new methods as may be found to be necessary to obtain the desired results. These studies would begin with studies to be conducted in the larger laboratory experimental animals, but with methods which could just as well be used in human beings. With experimental animals it will also be possible to cross check the results of the external counting methods to be used against more direct measurements using classical physiological methods, for the purpose of providing an absolute basis for calibrating the indirect methods. Contingent on how promising the procedures developed appear to be, clinical trials would follow.

The Medical Research Center is well equipped for initiating the proposed studies, both at the animal and at the clinical levels. The laboratories are especially well supplied with radiation detection and computing equipment.

Among the foreseeable additional equipment requirements is a second Anger camera for use in the proposed method for determining the blood volume with a tumor. The focusing collimators to be used with this would also have to be custom designed and constructed.

It is also desirable to modify the positron detector and to reprogram the method of data analysis used, to accommodate the more rapid rate of data acquisition that will be required and to improve the spatial resolution of the system. The existing version of the positron detector was designed for use in locating brain tumors. In its present configuration, a rigid ring of detectors, it is not easily used in the chest or abdomen. However, it can be rebuilt to provide the required capabilities. This would involve splitting the ring and providing a new method for holding it in position.

Animal Studies

With a view to developing applications in patients it seems necessary to get away from using the smaller laboratory animals such as mice and rats. Dogs, swine and rabbits are more appropriate. In particular, in the case of dogs, experience indicates that a supply of dogs with tumors is available through veterinarians in the local communities. These may be expected to include a variety of carcinomas and some sarcomas. For the present purposes there are advantages in working with spontaneously arising tumors rather than with transplanted ones in that the blood flow characteristics may be more like those encountered in patients. It is proposed that the development work on the methods mentioned above be conducted first using rabbits and normal dogs and measuring the blood flow rates in specific regions such as the liver.

Then dogs with tumors will be studied by comparing the blood flow rates in tumors with those in normal tissues.

Clinical Studies

When the methods have been checked out through animal studies and if the experience so gained indicates that a reasonable degree of success is to be expected in measuring the blood flow in tumors in human beings, such studies will be initiated. The protocols for such experiments, including calculations of and radiation doses that may be incurred by the patients will be developed as extrapolation from the animal experience.

Before being put into practice it is necessary that the proposed procedures be reviewed by a local clinical investigation committee. The established procedures at BNL for such review include obtaining assurance that written informed consent statements will be required for any subject to participate in the study, that except for explicity good medical reasons patients in the child-bearing ages will not be exposed to ionizing radiations, and that other safeguards of the patient's welfare will be strictly enforced. In all cases the exposures to radiation will be kept to the minimum consistent with obtaining the required data, and in any event below the exposure limits recommended by the ICRP, the NCRP, the AEC and by the local committees concerned with radiation protection. The approvals necessary forclinical investigation have not as yet been obtained because it is desired that the animal phase of the program be completed first so that in the proposal for clinical investigation the methods to be used and the protocols for the procedures can be described more definitively.

It can be expected that a wide variety of tumors will become available for study through referrals from physicians practicing in the local communities. Lung, abdominal and intracranial tumors are perhaps of the greatest interest for the proposed studies but valuable experience may also be gained by including skin cancers, breast tumors, and other more accessible tumors. To a large extent what can be done will be dependent on the type of patient that becomes available. This does not appear to be a severe limitation, however.

In general, the patients to be studied will be admitted to the BNL hospital for a few days and then returned to the care of the referring physician. Appropriate diagnostic procedures will be conducted to confirm the information received from the referring physician and to further define the tumors location before the blood flow measurements are attempted. When possible more than one of the methods under study will be used with a given patient. That is, if it is feasible to take measurements by two different methods with a single radioisotope administration, these will be done for comparison of the methods.

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4001031

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400103

1st YEAR BUDGET

Personnel		Proposed Grant Salary	% Effort
J. S. Robertson, M.D., Ph. D.		--	20%
H. L. Atkins, M. D.		--	10%
H. E. Hart, Ph. D.		--	8%
Laboratory Technician		9,000	100%
Laboratory Technician		8,600	100%
Secretary, (half-time)		3,500	50%
	Total Labor	$21,100	
Fringe Benefits @ 16%		3,400	
		$24,500	

Materials + Supplies		
50 Rabbits, 15 dogs and Maintenance		2,000
Isotopes		5,000
Expendable supplies		2,000
	subtotal	$ 9,000

Capital Equipment		
Anger Camera Nuclear-Chicago Pho-Gamma		40,000
	subtotal	$40,000

Technical Services		
Focusing Collimater System		$ 20,000
Modify Positron Detector for General Body Use		6,000
Interfacing of Nuclear Data System to "Brooknet"		38,000
Cyclotron time for ^{13}N		5,000
Computer Programming		7,000
Computer Time		2,000
Photography		1,000
	subtotal	$ 79,000

Travel	600
Hospital Services	---
General and Administrative costs at 35% of Direct Costs (not including Capital Equipment)	39,600
Total 1st Year Budget including overhead	192,700

ESTIMATED 3 YEAR BUDGET

	1st Year	2nd Year	3rd Year
Personnel	21,100	22,500	24,000
Fringe Benefits @ 16%	3,400	3,600	3,800
Materials + Supplies	9,000	9,200	10,200
Technical Services	79,000	29,000	15,500
Travel	600	600	600
Hospital Services	---	10,000	20,000
Subtotal	113,100	74,900	74,100
Overhead @ 35%	39,600	26,200	25,900
Capital Equipment	40,000	---	---
TOTAL	192,700	101,100	100,000

TOTAL 3 YEAR GRANT BUDGET: 393,800