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RECENT DEVELOPMENTS IN THE THEORY OF NEUTRON CAPTURE THERAPY

and

SYSTEMS FOR NEUTRON CAPTURE THERAPY: GENERAL CONSIDERATIONS

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PREFACE

This document consists of two accounts first written as internal reports in 1958 and 1959. Many of the ideas contained in the original reports have borne fruit, while others are apparently still of interest to workers in the field of neutron therapy capture. Accordingly it appeared advisable to combine and issue the reports for general distribution. The references have been up-dated.

RECENT DEVELOPMENTS IN THE THEORY OF NEUTRON CAPTURE THERAPY

by

Norman A. Frigerio

January, 1958

Interest in neutron capture therapy has centered, to date, on the use of the Li^6 and B^{10} (n,α) reactions.[1-4] This has been due primarily to two facts: they possess high thermal cross sections, and the reaction products have very short ranges and high ionization densities. Results have been encouraging, but difficulties of a chemical and physiological nature remain unsolved for these two nuclides. Ionic lithium and boron localize poorly in tumors, and lithium compounds which do not release ionized lithium under physiological conditions have not yet been synthesized. Boronic acid derivatives of the acid azo dyes such as Evans blue and trypan blue[5] have given promising results.[6] However, our recent experience with these two compounds has been that concentration of the dye in vivo is not accompanied by concentration of the boron, which appears to be hydrolyzed to free boric acid by enzymes in the organism before a high differential concentration can be achieved in the neoplasm.[7,8]

In considering possible activatable nuclides alternative to these it was first necessary to define the limits of our biological system. Since prime interest lies in human cancer therapy, we have based our calculations on the 70-kg "standard man" with a 1.5-kg brain.[9] In addition, for successful therapy, certain limitations must be placed on the system. First, it is necessary to provide the greatest possible radiation dose to the tumor cells, while providing the minimum possible dose to the non-neoplastic brain. Dose to the tumor stroma may be considered to be unimportant since, in the absence of a tumor, it is functionless in the brain. However, considerable evidence has been accumulated,[10] including studies of our own,[7,8] which indicates that many compounds localizing in brain tumors do not localize within the tumor cells but, rather, within the supporting stroma and vascular matrix. Hence, the thickness of the stroma may be critical in fixing the type and range of particles which may be employed. It has been suggested that ionic boron may be an exception,[11] and may localize to some extent within tumor nuclei.

The nature of the blood brain barrier[12] makes it likely that those chemical entities which will localize most strongly in the tumor, relative to the brain, will be strong, highly soluble anions of large molecular size, for example aryl sulfonic acids; hence, such compounds will be favored. The activatable nuclide, or the compound utilized to transport it to the tumor site, must be relatively nontoxic and must resist chemical or

enzymatic processes which would give rise to toxic products or which would result in conversion of the activatable nuclide to a nonlocalizing form. Also, from the standpoint of practical therapy, the activatable nuclide must remain concentrated in the tumor for a period long enough to allow efficient irradiation. Finally, the activatable nuclide should not itself constitute a source of radioactive body burden so large as to be dangerous. In view of experiences with internal emitters, a half-life lower limit of 10^9 years may be placed on nuclide stability.(13)

It has been demonstrated that the recoil energy of the neutron activation reaction is sufficient to free the activated nuclide from chemical bonds(14) releasing it into the surrounding matrix as an ion. Thus, to provide maximum tumor cell and minimum brain cell doses, the ratio of the physical half-life of the activated nuclide to its biological half-life in the tumor volume must be considerably less than one. Also, irrespective of the biological half-life of the activated nuclide, its physical half-life should be short enough to allow considerable control of therapy on the part of the therapist.

A further limitation is placed on the physical characteristics of the activated nuclide by consideration of the maximum and minimum particle ranges which may be tolerated in the practical case. Thus a particle with a range of 10 microns or less (a 3-MeV α particle) might well expend most of its energy within the tumor stroma, reaching, at most, only the first layer of tumor cells, while particles with ranges of the order of 60 to 100 microns (certain fission fragments) would probably blanket stroma and tumor cells very well. At the other extreme, particles with ranges up to 10,000 microns (a 3-MeV β particle) might still be very useful in man since this distance from the outer edge of the stroma would encompass a non-neoplastic volume of cells considerably smaller than would be removed by surgical resection. Because the dose per unit mass for such long-range particles would decrease very rapidly with increasing distance from the tumor surface, the limitation on total dose to normal tissue could still be encompassed. In addition their long range and lower specific ionization would result in a more uniform dose deposition within the tumor, ensuring against the survival of a few aberrant cells. Such considerations have undoubtedly been operative in the successful therapeutic use of such β-emitting isotopes as P^{32}, I^{131}, Au^{198}, Ta^{182}, etc., and the α- and β-emitting astatines.

High energy photons, emitted by activated nuclides in the form of γ rays or electron capture x-rays, have generally been assumed to be of negligible consequence in neutron capture therapy, and the low specific ionization of such photons justifies such assumption. In certain cases, however, their effects may not be negligible. For example the 0.48-MeV gamma produced by the B^{10} (n,α) process possesses a relatively high absorption coefficient in tissue. If it originated in a central brain tumor,

such a photon would, on the average, deposit well over 31% of its total energy within the skull of a human subject. Such a contribution to the total dose given normal tissue might well prove significant in many cases.

Such high energy photons might also tend to aid the differential irradiation of the tumor cells. So long as the photons originated primarily within the tumor, the dose per unit mass of tumor tissue would be relatively uniform, while the dose per unit mass of normal tissue would decrease inversely as the square of the distance from the tumor surface. This situation is closely analogous to that obtaining in the well-focused radiation teletherapy of localized tumors. The presence of high energy photons would also afford the therapist an excellent measure of the instantaneous dose and dose distribution during treatment since they could be easily measured and located with appropriate scintillation detectors. This latter consideration would be particularly applicable to the 6- to 8-MeV γ rays characteristic of (n,γ) nuclear processes since their absorbtion coefficients in tissue are quite low.

In discussing the dose delivered to tissue, both normal and neoplastic, by neutron activation processes, it is profitable to consider certain parameters of the interaction of neutrons with matter. Among those of interest are:

σ	The probability of interaction, usually called the microscopic neutron cross section, in barns (1 barn = 10^{-24} cm^2).
N	The atom density, in atoms/cm^3.
N^1	The activatable atom density, in atoms/cm^3.
n	The neutron density in n/cm^3.
v	The neutron velocity in cm/sec.
t	The total neutron irradiation time in seconds.
x	Thickness, normal to (nvt), in cm.
A	The activated atom density, in atoms/cm^3.
Q	The total energy yield for a nuclear process, in MeV.
E	Particle energy, in MeV.
D	The total dose per unit volume, in MeV.
ξ	The average loss in the logarithm of the neutron energy per collision.
$\int_{E_1}^{E_2} \frac{\sigma_a dE}{E}$	The activation integral for nonthermal pile neutrons, in barns. Energies here are expressed in eV.

With the subscripts:

a	Indicating activation.
γ	Indicating photon.
p	Indicating charged particle.
s	Indicating scattering.
θ	Indicating thermal neutrons, i.e., those neutrons in equilibrium with matter at a temperature of 293.17°K.
f	Indicating fission process.
n	Indicating incident neutron.
c	Indicating elastic collision.
t	Indicating total.

Employing these definitions it can be shown that the total number of atoms activated per unit volume, A, by neutron capture in a given system, is given by the expression:

$$A = (nvt)\left(1 - e^{-N^1 \sigma a^x}\right) \tag{1}$$

and that the total energy released per unit volume is simply AQ_a. Whether or not AQ_a is equal to the total dose per unit volume, D_a, depends on whether or not all of the energy released is dissipated within an infinitesimal distance from the site of activation. Of all the activation processes considered (see Table 1), D_a would most nearly equal AQ_a only for the Li^6 (n, α) and He^3 (n,p) reactions since each of the others produces at least one photon or other long-range particle. Hence, D_a must be calculated by integrating AQ_a over the entire significant dose volume for each of the modes of energy release involved.

The total energy released per unit volume, Q, due to collision processes with neutrons, may be given, for low values of x, by the expression

$$Q_c = E_n\,(nvt)\left(1 - e^{-\xi}\right)\left(1 - e^{-N\sigma_s x}\right) \tag{2}$$

In tissue the total collision dose per unit volume, D_c, will be essentially equal to Q_c since the atoms to which the neutron energy is transferred will ionize and, consequently, display very short ranges and high specific ionizations.

For normal tissue the values of N and N^1 have been defined for the "standard man"[9] for all of the biologically significant elements with the exception of boron. For purposes of computation we have taken a value of 0.4 parts boron per million parts of tissue as being the best average value for man.[15] Values for σ are known with considerable accuracy.[16] x, nvt and tissue density may be taken as equal to one so as to normalize

Solution of Equation 1 for total activation dose, D_a, yields a value of 7.5×10^{-9} ergs/cm^3 for a unit thermal neutron density (i.e., nvt = 1). Similar calculations have also been made employing other models with essentially similar results.[17-20] Since the activation cross sections of each of the biologically significant activatable nuclides is inversely proportional to the neutron velocity,[21] the appropriate activation integrals may readily be calculated for nonthermal pile neutrons. From these the total activation dose due to a unit density of these neutrons is found to be 9×10^{-9} ergs/cm^3. For a unit density of 100 eV neutrons, a value chosen as representative of the resonance region of neutron energies (0.3 to 3000 eV), the calculated activation dose is 1.2×10^{-10} ergs/cm^3. This dose decreases monotonically with increasing neutron energy.

The collision dose, D_c, may similarly be calculated employing Equation 2, although, of course, the collision dose from purely thermal neutrons will be zero. For a unit density of 100 eV neutrons the collision dose will be 2.2×10^{-11} ergs/cm^3 and this dose increases nearly monotonically with increasing energy.[21] Nonthermal pile neutrons, will, because of the nature of their energy spectrum, yield a real collision dose whose value will generally be higher than that of equivalent resonance neutrons. The precise value will be strongly dependent on the geometry and materials of the facility in which they are generated.[21] From these values it may be seen that minimum total tissue dose will be delivered by monoenergetic resonance region neutrons rather than by thermal or a nonthermal pile neutron spectra.

In addition, scattering computations employing expressions of the form of Equation 1 indicate that penetration of resonance region neutrons is considerably greater than that of thermal neutrons,[20,22] lessening depth dose problems. This combination of lowered tissue dose with smaller flux attenuation should be decidedly advantageous in obtaining a high dose ratio between tumor and normal tissue.

Although such computations are very useful for predictive purposes, the simplifying assumptions employed in their derivations occasion the introduction of errors undesirable to the therapist.[23] Accordingly we have developed a series of true tissue equivalent materials[23] and ionization chambers for dosimetry in neutron capture therapy.[24] These materials can be easily compounded to duplicate precisely the C, H, O, N and minor element composition of any chosen tissue and are readily molded into any form or size for the measurement of depth doses. They can very easily be formulated to include radionuclides for internal calibration and activatable nuclides can be included in any concentration or spatial concentration distribution for the replications of conditions obtaining in practical neutron capture therapy.

In examining the available nuclides for possible use in neutron capture therapy, relative tumor and tissue doses could be calculated if

N^1 were known. Since N^1 will depend on the complex biological and chemical parameters of the compounds and the tissues comprising the system, it would be impossible to predict it a priori. It could only be obtained by actual measurements of the temporal and spatial distribution of the activatable nuclide in vivo. For practical purposes, however, certain limits may be placed on N^1. Biologically even the least toxic of substances will cause death in concentrations greater than about 0.2 moles/kg.[25] Hence it is unlikely that N^1 for activatable nuclides could ever exceed 10^{20} atoms/cm^3. Also, at least for certain classes of promising compounds, biochemical considerations make it probable that N^1 will be reasonably constant irrespective of the nature of the nuclide. Therefore, to a first approximation, nuclides may be compared as to potential usefulness on the basis of some parameter independent of N^1. We have chosen to consider $\overline{Q}_p \sigma_a E$, the product of the average particle energy yield and the activation cross section at neutron energy E, because of the ready availability of the necessary data[9,17] and of the direct relationship of this quantity to the delivered dose. Values of $\overline{Q}_p \sigma_a E$, and other pertinent values, for a number of potentially useable nuclides are given in Table 1. Since the effective value of $N\overline{Q}_p \sigma_a, \theta$ for a unit mass of normal tissue is 2×10^{21} atom-MeV-barns, and since the additional activation dose should at least equal the normal tissue dose for effective therapy, $\overline{Q}_p \sigma_a E$ should exceed 20 MeV-barns with N^1 taken at 10^{20} atoms/cm^3.

In practice only those nuclides whose maximum values for $\overline{Q}_p \sigma_a E$ exceeded 100 have been considered to help ensure adequate D_a with lower values of N^1. In addition, because of the impossibility of predicting biological half-lives for the many possible chemical forms of the activatable nuclides, we have chosen to limit our consideration to those activated nuclides with physical half-lives of less than 100 hours.

Examination of the table reveals that, for thermal neutrons, the U^{235} fission process possesses the highest $\overline{Q}_p \sigma_a \theta$ product. In addition the particles are released promptly and have extremely high specific ionization values and ranges (40 to 60 μ) which seem ideal for therapy, in view of the limitations imposed by stroma penetration and normal tissue dose. While the fission products which are released by the process display relatively long decay constants, their total decay energy is only about 10% that of the prompt energy. In addition pretreatment of the subject with certain chelating agents[28] might decrease the effective biological half-life of these products, decreasing thereby the total energy expended within the organism. This same principle could, of course, be extended to long-lived states of any activated nuclide.

In the thermal region the other processes of interest can be seen to be the 3 (n, α) reactions, although the Eu^{151} and Dy^{164} (n, γ) processes would warrant consideration if chemical conditions were favorable.

Table 1

ACTIVATION PARAMETERS OF CERTAIN NUCLIDES

Activatable nuclide[a]	Natural abundance, %	$\sigma_a \theta$,[b] barns	σE_n,[c] barns	E_n of maximum resonance, eV	$\int_{0.17}^{\infty} \frac{\sigma_a dE}{E}$, barns	Particles produced	$\overline{Q}_p$,[d] MeV	$Q\gamma$,[e] MeV	Maximum energy of significant decay photons, MeV	$\sigma_a \theta \overline{Q}_p$, barns MeV	$\sigma E \overline{Q}_p$,[c] barns MeV	$\int_{0.17}^{\infty} \frac{\sigma_a dE}{E} \overline{Q}_p$, barns MeV	T 1/2 of activated nuclide,[f]
He^3[g]	0.017	6080			6480	p, T^3	0.77			4,680		5,000	Prompt; 12.5y
Li^6[g]	7.52	1065			1135	α, T^3	4.8			5,130		5,450	Prompt; 12.5y
B^{10}[g]	18.8	4520			4800	α, Li^7	2.4		0.48	10,800		11,500	Prompt
As^{75}	100	4.6	1,010	4.6	31.5	β^-	1.2	7.3	1.2	5.5	1,210	38	26.3h
Br^{79}	50.52	12.9	1,700	35	133	$\beta^-\beta^+$	0.74	7.8	0.05	9.6	1,260	100	4.6h→18m
Br^{81}	49.48	4.0	770	100		β^-	0.18	7.8	1.3	0.7	138		35.9h
Rh^{103}	100	171	5,000	1.3	589	β^-	0.96	6.8	0.9	164	4,800	567	4.3m→44s
Ag^{107}	51.35	50	640	18	98.3	β^-	0.55	7.3	0.6	28	350	54	2.3m
Ag^{109}	48.65	100	13,100	5.2		β^-	1.11	6.5	0.7	111	14,500		24s; 270d
In^{115}	95.77	214	30,000	1.5	2580	β^-	1.23	6.5	2.0	263	37,000	3,180	13s; 54m
Sb^{121}	57.25	6.3	1,400	6.2	147	β^-	0.71	6.8	0.6	4.5	1,000	105	3.5m→67h
Sb^{123}	42.75	2.8	1,300	22	125	β^-	1.07	6.4	2.0	3.0	1,400	134	1.3m; 21m; 60d
I^{127}	100	6.2	185	38	119	β^-	0.74	6.6	0.4	4.6	137	88	25m
La^{139}	99.91	9.5	173	71		β^-	1.42	5.1	2.5	13.5	246		40h
Sm^{152}	26.63	158	15,000	8.2	1559	β^-	0.30	5.4	0.5	48	4,500	468	47h
Eu^{151}	47.77	1400	11,500	0.45	842	β^-	0.69		0.3	970	7,950	580	9.2h
Dy^{164}	28.18	2610	7,700	5.4		β^-	0.46	6.5	0.8	1,200	3,540		1.3m→139m
Ho^{165}	100	68	5,100	3.8		β^-	0.70		0.08	48	3,570		27.3h
Ta^{181}	100	24	13,000	4.3	517	β^-	0.20	6.1	1.2	4.8	2,600	104	16.5m→111d
W^{186}	28.4	38	15,000	18	320	β^-	0.49	6.5	0.7	18.7	7,350	157	24h
Re^{185}	37.07	113	3,500	2.2	1061	β^-	0.39		0.1	44	1,360	417	90h
Ir^{193}	61.5	147	5,800	1.3	1213	β^-	0.81	7.3	0.3	119	4,700	985	19h
Au^{197}	100	111	30,000	5.0	1300	β^-	0.51	6.5	0.4	56.5	15,300	663	65h
Th^{232}	100	8.3	2,300	23	81.3	β^-	0.45	5.1		3.7	1,030	36.6	23.3m→27.4d
U^{235}[h]	0.715	655	320	9.0	290	(h)	168	12	8	110,500	53,800	48,700	Prompt; (h)

[a] Certain natural mixtures of high cross section have been omitted because of uncertainty as to the nuclides responsible and their characteristics.
[b] Where otherwise unavailable thermal cross sections have been obtained by multiplication of the 2200 m/s values by $\frac{2}{\sqrt{\pi}}$.(21)
[c] Although σ_t, rather than σ_a, is given, only those nuclides have been listed for which it was reasonable to assume that σ_t was effectively equal to σ_a.(16)
[d] In calculation of the average β^- energy a Fermi distribution has been assumed.(26)
[e] Calculated from the available mass differences.(27)
[f] Sequential isomeric states are indicated by an arrow. Effectively independent isomeric states have been listed in order of probable importance in activation.
[g] For these nuclides it has been assumed that σ_a is proportional to $E_n^{-1/2}$ and $\int_{0.17}^{\infty} \frac{\sigma_a dE}{E}$ calculated accordingly.
[h] All values given are for the fission process. Since the fission products decay approximately as $T^{-1.2}$, no half-life can be given.

In the resonance region, however, the significant processes are of the $(n,\gamma)\,\beta^-$ type. Some of these reactions, indeed, have $\overline{Q}_p\,\sigma_t\,E_n$ products exceeding that of the $B^{10}\,(n,\alpha)$ reaction and appear to hold considerable promise. This is particularly so since many of these elements enter into chemical forms highly suitable for tumor localization more readily than either Li^6 or B^{10}. Their generally sharp resonances suggest the use of monoenergetic resonance region neutrons with the consequent dose advantages outlined above.

For the sake of completeness nonthermal pile neutron activation integrals have been included where available, although it can be readily seen that they offer little advantage compared to either thermal or resonance neutrons.

The naturally high concentration of I^{127} in the thyroid presents a unique case among activatable nuclides. As a consequence of this concentration, and of the short half-life of the I^{128} produced, doses of

6×10^5 ergs/g or more could be delivered to the thyroid in a few hours with available resonance neutron sources. Total dose to other tissues in the same interval, would be negligible by comparison. Employment of activation therapy of thyroid neoplasms and of thyrotoxicosis would remove many of the current objections to I^{131} injection therapy. The short half-life of I^{128} would result in better control of dose by the therapist and much lower total body doses. The reduced iodine uptake of many neoplasms of thyroid origin would be of less consequence with activation therapy since the subject could be treated continuously with normal iodine until sufficiently high tumor concentrations had been achieved without incurring any radiation damage. It would even be possible to treat those tumors which had lost all vestiges of iodine uptake so long as they retained some of the natural iodine which had been present before onset of neoplasia. Certain recent studies of our own on human thyroid tumors have suggested that I^{127} may be retained in the tumor mass well after uptake ability has been lost.(8)

For use in capture therapy, neutron sources must possess at least two attributes; high flux and freedom from contaminating ionizing radiation. Collimation of the neutrons into a beam would also be desirable. For neutrons with thermal or epithermal spectra, fission reactors appear to be the most practical of the current sources. Thermal fluxes in excess of 10^{11} n/cm^2 sec can easily be obtained from small, relatively inexpensive reactors.(29,30) With D_2O employed as moderator and Bi shields such reactors would have very low associated gamma fluxes. These same units can also be employed as sources of nonthermal pile neutrons with appropriate filtration, although at some loss in available flux. Since the $Li^6(n,\alpha)T^3$ reaction produces no photons, lithium filters or lithium deuteride moderators would best fit the low gamma requirements of biological facilities.

For the production of monoenergetic resonance neutrons, charged-particle accelerators appear to be the sources of choice. By employing charged particle reactions of high yield, low threshold energy and very low photon contamination, such as certain of the (p,n) and (d,n) processes,(31,32) large numbers of monoenergetic neutrons can be obtained using the relatively inexpensive 2- and 3-MeV Van de Graaff accelerators. Such systems also allow extremely precise and flexible control of neutron energies. Advantage may be taken of the preferential forward scattering of certain processes, such as the $T^3(p,n)He^3$ reaction, and of close proximity of target to subject, to obtain neutron fluxes requiring little, if any, further collimation for therapeutic use.

Besides the physical parameters of the neutron capture system, certain biochemical considerations must also be satisfied. As was stated above, the chemical form of the activatable nuclide in vivo must be localizable in the neoplasm, stable to biochemical attack, and nontoxic to the organism. Since only a few of the simple ions of the potentially useful nuclides appear to fulfill these criteria, our attention has been turned to

molecules containing the appropriate nuclides but possessing chemical properties better suited to the therapeutic requirements.

The difficulties inherent in the employment of ionic boron and boronic acids have already been noted, and it seemed that boron might be more successfully employed if it was bound in a nonionic and hydrolytically stable form. The synthesis of boron-containing compounds, so sterically hindered as to be completely nonhydrolyzable under physiological conditions, has recently been reported.[33-35] The synthesis of sulfonated derivatives of these hindered boron compounds is currently being pursued in our laboratories, and, while theoretically feasible, has so far proved practically difficult.

In considering other chemical possibilities we have turned our attention to chelate compounds. Protoporphyrin,[36] hematoporphyrin, and substituted alkylene-diimino and Pfeiffer[37, 38] complexes of uranium have proved, in our hands, to be too toxic for serious consideration. Since the modes of death observed, in mice, were identical with those observed with uranyl ion poisoning,[39] it can only be assumed that the dissociation constants of these chelates were insufficiently low to prevent release of toxic amounts of uranyl ion to the organism. Accordingly it seemed necessary to obtain compounds of even lower dissociation, such as the metal phthalocyanines.[40] It has been reported that these compounds possessed dissociation constants too low to be measured with even the most sensitive radioisotope techniques.[41-43] We have confirmed these observations, resynthesizing many of the phthalocyanines previously reported[44,45] and have succeeded also in synthesizing certain of the group I B, III B, VIII, lanthanide and actinide phthalocyanines which are of interest for neutron capture therapy.[46]

Methods developed for the synthesis of these phthalocyanines have included fusion with phthalonitrile, metathesis with dilithium phthalocyanine and reaction with urea and phthalamide. They are deep blue or green solids possessing strong purple reflexes. They apparently contain one atom of metal per phthalocyanine residue, and decompose in vacuo at 350 to 500°C to yield the metal-free phthalocyanine as a sublimate. They are soluble in concentrated sulfuric and fluosulfonic acids from which they may be reprecipitated by dilution; such treatment results in the slow decomposition of some of these compounds. The lanthanide phthalocyanines, are somewhat soluble in such organic solvents as dimethyl formamide, and all of the phthalocyanines are very slightly soluble in quinoline, pyridine and chloronapthalene.

In consequence of this insolubility in aqueous media it has been necessary to prepare solubilized derivatives of these compounds for toxicity and localization tests. The nature of the blood-brain barrier, and biochemical considerations of toxicity, dictated the use of sulfonated derivatives and

many of them have proved readily preparable.[47-52] For others, however, considerable difficulty has been encountered, particularly in preparing samples of pharmaceutical purity. With the advent of sulfonating agents more effective then fuming sulfuric acid, however, progress is again being made.

The alkali phthalocyanines have also been prepared[45] but have proved to hydrolyze in aqueous media. The dilithium compound alone has been found to hydrolyze, under certain conditions, at a rate compatible with therapeutic usage.[53] In the hope of obtaining sufficient steric hindrance to inhibit hydrolysis completely, as with the boron compounds aforementioned, we have turned our efforts toward synthesizing dilithium phthalocyanine analogs with hindering groups or bridges extending over the central ring. While chemically feasible, this approach has proved practically difficult, for the most part because the problem of the synthesis of requisite intermediates must first be solved.

The compound of greatest potential utility appears to be the sulfonated uranyl phthalocyanine. This has been prepared,[8,47-52] although in poor yield, and its pharmacological properties have been examined. The minimum lethal dose (intravenous) for mice is over 1000 mg/kg, and doses in this range are without apparent effect on the health or breeding ability of the recipient mice or of their offspring. Localization in brain tumors has been striking, with differential concentrations of 50 and over having been achieved routinely. In addition, all of these compounds are highly colored, greatly simplifying location of the tumors.

In consequence of such favorable pharmaceutical properties a number of other phthalocyanines containing both activatable and nonactivatable nuclides, have been prepared in the colloidal form and in the form of the sulfonated analogs. These compounds show considerable promise as radiological contrast media; gamma- and positron-emitting diagnostic aids;[54,55] vital dyes for sequential light[56] and electron microscopy of unfixed cells; activated or activatable nuclide carriers for cell physiology studies or for selective inter- and intracellular irradiation; carriers for neutron coherent scattering studies; sources of carrier-free radionuclides;[43,57] and carriers of fission products and other radionuclides for radiation damage studies free of concomitant chemical toxicity problems. The intense color of the sulfonated analogs and the very slow excretion of these compounds from the organism via the bile ducts, which we have observed,[7,8] suggest their use in physiological studies of this system. The easily-prepared colloidal forms of the unsulfonated compounds should also serve in the neutron capture irradiation of organs and cavities where such colloids normally localize.

Synthesis of phthalocyanines containing both electronegative and electropositive activatable nuclides such as the hexadecabromo-metal-phthalocyanines, have proved feasible in our hands and result in molecules

of greatly enhanced $\sigma_a \overline{Q}_p$ values. As a corollary to this approach it should be feasible to synthesize analogs of compounds which have been reported[58-60] to localize in somatic, as well as cranial tumors. Biochemical considerations suggest, for example, that properly brominated analogs of the porphyrins, pteroylglutamates and naphthoquinones should localize in tumors as well or better than the parent compounds and, in addition, provide opportunity for neutron activation therapy.

In conclusion it may be said that the general synthesis of nontoxic, nuclide-containing compounds whose biochemical properties are essentially independent of the nature of the key nuclide provides physicians with a number of useful research and diagnostic tools. In addition, the combination of the biochemistry of such compounds with the physics of the thermal and the resonance neutron activation of the contained nuclides presents a highly promising, rational approach to the therapy of neoplastic and other radiosensitive disorders.

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SYSTEMS FOR NEUTRON CAPTURE THERAPY: GENERAL CONSIDERATIONS

by

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Neutron capture therapy may be considered as a form of radioisotope therapy wherein activation of the key nuclide is effected only after its localization within the lesion. The use of compounds that are localized relatively slowly or with poor specificity is permitted without incurring the whole-body doses which are often limiting in conventional radionuclide therapy. The safety precautions and speed required in the synthesis, handling and administration of radioactive compounds are obviated, and dose parameters may be varied during therapy by external control of the slow-neutron flux. Secondarily, the nature of the neutron capture process permits the use of hitherto unavailable nuclides of very short half-life and very high specific energy output, markedly broadening the armentarium of the radiotherapist.

The possibility of applying neutron capture reactions to therapeutic problems was originally envisioned by Locher[1] and later investigated by Kruger, Zahl and others.[2-7] To date interest has centered primarily on the Li^6 and B^{10} (n, alpha) and U^{235} (n, fission) processes, all of which are most effective with neutrons of thermal energies. The extreme toxicity of ionic uranium has precluded its serious consideration, but encouraging results have been obtained with Li^6 and B^{10} in mouse and human brain tumors. The high thermal capture cross sections of these nuclides has allowed their selective activation among the nuclides characteristic of tissue. The high ionization density, prompt emission and short range of their reaction products has also permitted the delivery of intense radiation dosages where physiological conditions permitted their localization within closely circumscribed tumor masses.

Nevertheless, chemical, physical and physiological difficulties have been encountered in the treatment of brain tumors, and the full promise of capture therapy does not seem to have been realized in practice. The penetration of thermal neutrons into tissue is poor, and considerable difficulty has attended attempts to obtain optimum flux density in tumor masses removed from the irradiated surface.[5,8] Ionic lithium possesses a relatively low chemical toxicity but is only poorly localized in the tumors. Borates localize only moderately well in the tumors and then only for short time intervals after injection. Recourse to very critical irradiation schedules has been necessary coupled with intracarotid infusion of amounts so large as to present severe surgical and toxicological problems. These problems

arise partly because of the chemical toxicity of the compounds themselves and partly because of rapid concentration of the boron in the skin. Subsequent neutron capture leads to the development of acute radiation burns.[5]

Promising localization, coupled with low toxicity, has been observed with boronic acid derivatives of the acid azo dyes, e.g. Evans and trypan blue.[6,9] In our experience with these compounds, however, localization of the dye in mouse brain tumors is not accompanied by parallel localization of the boron. The evidence obtained[10] seems to indicate an enzymatic hydrolysis of the compounds to yield free borate anions before selective concentration is achieved. In any case, these dyes have failed to provide significant regressions in mouse tumors irradiated with high fluxes of thermal neutrons.[11] The simpler boronic acids can also be synthesized in forms of low chemical toxicity, but these have also failed to yield selective tumor boron concentrations significantly higher than those obtained with the inorganic borates.[12,13] This observation suggests that they are also hydrolyzed by the organism before localization is effective.

In considering alternatives to these systems, a broad survey has been made of processes and materials available for neutron capture therapy, and a number of promising alternative systems have been developed and tested for feasibility. Theoretical considerations appropriate to these systems are discussed below.

Tissue Neutron Populations

The basic aim of radiotherapy is the delivery of a curative dose to lesions without damaging normal tissues. Thus, dose measurements and computations are required both for the lesion and for normal tissue. In neutron capture therapy the computation of such doses requires a precise knowledge of the energetic and spatial distribution of the total neutron population. Since the composition and geometry of the majority of human lesions effectively obviates the use of the simpler diffusion or transport approximations for the general computation of neutron dispersion, we have had recourse to Monte Carlo methods and to direct activation measurements.[14] The measurements are being accomplished with the aid of true tissue-equivalent gel systems which we have developed. These systems permit dose measurement under a very wide range of concentrations and spatial dispersions of activatable nuclides in systems which are physical simulacra of human organs.[15]

Until Monte Carlo calculations have been completed, use may be made of some simple approximations to define the limits of neutron capture therapy systems. In the human, the distance from a lesion to the nearest body surface will generally range from 0 to 20 cm, and the distance to the furthest surface will seldom exceed 2 meters. The focusing of neutrons does not appear feasible, so we will assume that irradiation is accomplished with a

narrow, plane-collimated beam normal to the body surface closest the lesion. The use of such beams is standard practice in current radiotherapy because it minimizes damage to normal tissue. Where the geometry permits, rotation therapy may be applied, further lowering the dose to normal tissues. Of course, any beam broadens with increasing tissue penetration because of scattering processes, and this effect is about tenfold more pronounced for neutrons than for photons. Nevertheless, a broadened beam does not approximate the semi-infinite condition until relatively large penetrations are reached, and the beam approximation is the most useful for the range of penetrations envisioned in human therapy.

Three types of neutron energy distributions appear to be available for application to neutron capture therapy. Those may be characterized as the thermal distribution, the "pile" or "dE/E" spectrum, and those very narrow distributions which are effectively monoenergetic.[16]

Thermal neutrons are characterized by a Maxwell-Boltzmann energy distribution, and their effective temperature in tissue is raised only slightly above the ambient by capture in the normal tissue nuclides. For such neutrons the flux density may be given as a function of distance from the irradiated surface, x, by

$$(nvt)^{\theta} = (nvt)_0^{\theta} \; e^{-\Sigma_r^{\theta} x} \qquad (1)$$

where Σ_r^{θ} is the macroscopic, thermal (θ), removal (r) cross section, and $(nvt)^{\theta}$ the thermal flux density. For a narrow beam of thermal neutrons incident on a plastic phantom approximating a human head, Σ_r^{θ} was found to be 0.40 cm^{-1}[8] for "tissue" of density $\rho = 1.06$ g/cm^3. For an infinite beam normally incident on a semi-infinite tissue slab, a comparable value of 0.52 cm^{-1} has been obtained by Monte Carlo calculation.[17,18] From these latter studies it also appears that the neutron density is a hyperbolic rather than exponential function of distance, but the difference is negligible at penetrations in excess of 0.5 cm.

If any tissue region, such as a lesion, also contains an activatable nuclide, the number of activated atoms per unit volume, N_a, may similarly be given by:

$$N_a = \frac{\Sigma_a^{\theta} (nvt)_0^{\theta}}{\Sigma_t^{\theta}} \left[e^{-\left(\Sigma_r^{\theta} x\right)} - e^{-\left(\Sigma_r^{\theta} x + \Sigma_t^{\theta} h\right)} \right] \qquad (2)$$

where h is the thickness of the lesion along the beam path, and the subscripts 0, a and t denote initial, activation and total respectively. Values for

the microscopic thermal cross sections, σ^{θ}, are readily available,[19] and measurement of the activatable atoms per unit volume, N_A, by available chemical and physical methods permits calculation of Σ^{θ}. In practice, the uncertainties in N_a are determined primarily by the uncertainties in Σ_r^{θ}.

For neutrons of energy greater than thermal, data on σ_t are also available but, because of the marked and often very complex dependence of σ_t on E_n, expressions of the form of Equation 2 are not very useful. In addition, such neutrons lose energy rapidly but discontinuously while traversing tissue. The complexities introduced by the combination of neutron moderation and rapidly varying neutron cross sections render it probable that only Monte Carlo methods or the method of moments will suffice for adequate solutions. This is particularly true of slow neutrons in the human body. The dimensions of the body encompass a range of relaxation lengths, which invalidates the boundary condition approximations of diffusion or transport theory. Hence, precise expressions await the completion of appropriate analyses and computer programs.

Nevertheless, available measurements and Monte Carlo studies[14,17] indicate that the epithermal activation of nuclides in tissue follows a pattern similar to that of Equation 2 with a much more pronounced hyperbolic form and markedly lower Σ_r values. This was verified experimentally. Thin gold foils were placed at intervals along the long axis of a cylinder of tissue-equivalent gel whose dimensions approximated those of the human head. The cylinder was completely encased in cadmium and exposed to a plane-collimated beam of pile neutrons directed along the long axis. The activation curve was characterized by a hyperbolic peak at 3.5 cm penetration, followed by an exponential decay of $\Sigma_r = 0.16\ cm^{-1}$. Thus at 10-cm penetration, activation was 61% of its surface value. A thermal activation curve was obtained in the same manner by omitting the cadmium casing. Here the value at 10-cm penetration was less than 1% of its surface value. The ratio of these two activation values continues to increase rapidly with increasing distance. Since the maximum dose to normal tissue for neutrons in the resonance capture region (0.07 → 250 eV) is only about 3.5 times the maximum thermal dose,[17] use of these neutrons provides a method of greatly increasing the ratio of lesion dose to tissue dose.

With nuclides which show "1/v" (that is, the cross section is inversely proportional to the neutron velocity) behavior and possess no capture resonances, a similar improvement in dose ratio cannot be expected since the normal tissue nuclides responsible for slow neutron dose are also of the "1/v" type. Nevertheless, some improvement is available. The total cross section for "1/v" nuclides, integrated over a dE/E spectrum above 0.07 eV, is 1.2 times the thermal (0.0253 eV) cross section.[16] These increased epithermal cross sections for "1/v" nuclides, coupled with the greater penetration of epithermal neutrons, serve to render this combination more attractive than the use of purely thermal neutrons with "1/v" nuclides. Thus,

at 10-cm penetration into a semi-infinite tissue slab,[17] activation of even a "1/v" nuclide by 100-eV neutrons is 27% of its surface value compared to less than 1% for thermal neutrons.

For nuclides with pronounced capture resonances, Monte Carlo studies[14] have indicated that narrow beams of monoenergetic neutrons, even when broadened and moderated by passage through tissue, should prove more useful than a filtered pile spectrum. The major portion of the pile spectrum consists of neutrons of energies below that of the optimum capture resonances,[16] and a relatively poor utilization of the total flux for capture results. Fluxes of monoenergetic neutrons, on the other hand, can be produced at energies optimum for activation of the selected nuclide and yielding maximum capture utilization of the flux and minimum tissue dose. Calculation of the optimum neutron energy value will depend on the characteristics of the chosen nuclide and the geometry and physiology of the lesion. While such computations do not lend themselves to facile general solutions, they may be attacked by moments, Monte Carlo, or transport methods. To a first approximation, neutron age theory indicates that the optimum energies should lie within a range of 1 to 4 times the energies of the chosen resonances.[20,21] As an example, a lesion close to the body surface and containing Au^{197}, whose principal resonances are at 4.9 and 61.5 eV, would best be activated with a beam containing neutrons of 6 and 65 eV. As the lesion depth increased to approximately 1.1 cm the optimum energies would rise to values of approximately 20 and 250 eV. At distances in excess of this the tissue neutron distribution would rapidly approach the dE/E spectrum treated above, with the optimum energies remaining fixed but with an effective penetration markedly greater than that characteristic of the dE/E spectrum. In general, optimum nuclide activation is to be expected with nuclides possessing strong capture resonances irradiated by monoenergetic neutron beams of energies appropriate to the resonances and to the geometry of the lesion.

Process Characteristics

Neutron capture processes are almost invariably accompanied by photon emission and resultant recoil of the activated nucleus. The recoil energies for normal tissue nuclides lie in the range of 600 to 6000 eV. As these values represent less than 0.1% of the total energy release, their contribution to the total dose may often be neglected. Such energies, however, are far higher than the corresponding chemical bonding energies of the activated nuclides. The nuclide ion is promptly liberated and rapidly loses its recoil energy and eventually comes to rest within a few angstroms of its origin, either as the free ion or chemically bound to a compound newly formed in the matrix. To prevent irradiation of normal tissue by the decaying nuclide, its rate of diffusion or biological transport from the tumor into normal tissue, whether in ionic or compound form, must be much lower than its physical decay rate.

Ideally, secondary decay processes (fission products, delayed isomeric transitions, etc.) should also fulfill this condition. Where this is impossible, the rate of excretion of secondary products should be higher than the rate of decay. In this way, the secondary process, while not contributing to the dose to the lesion, would at least contribute little to the dose to normal tissue.

Irrespective of excretion rates, the convenience of the therapist dictates a short physical half-life. With an activated nuclide of short half-life, the dose rate to the lesion would closely follow the rate of neutron irradiation, giving the therapist better control of the dose rate and greater freedom in scheduling exposures. Should the activatable nuclide chosen be itself radioactive, it should not constitute a source of radioactive body burden great enough to present a greater threat than the lesion. Special surgical techniques would probably permit the infusion or implantation of nuclides of short half-life (Na^{24}, Au^{198} and I^{131} are now being used), without incurring unreasonable body burdens. However, for simple injection techniques, present experience with internal emitters suggests the use of nuclides with half-lives in excess of 10^8 years.

Further limitations may be placed on the selected process by consideration of the nature of the decay products with respect to their range and energy loss in tissue. The diameter of most human cells lies between 5 and 50 μ, with intercellular distances of the same order. The nucleus probably constitutes the major radiosensitive volume of the cell,[22] and, since it is generally much smaller than the cell, a single ionizing particle with a range of 5μ or less possesses a low probability of traversing it.

All of the ionizing particles under consideration have a range of more than 1 μ. Therefore, if each μ^3 of tissue has the same concentration of activatable nuclide, the energy deposited by the particles will be completely uniform throughout the tissue. Assumption of such uniformity is probably unrealistic for many practical cases, and nonuniform distribution of the nuclide would require the use of particles with a longer range to obtain uniform distribution of energy.

We may envision a "typical" tumor as consisting of a biphasic growing edge and a monophasic, necrotic core.[22] The outer phase of the growing edge consists of neoplastic cells tightly packed into small volumes, each delimited by the stroma. The density and oxygen tension of the stroma decrease rapidly with increasing distance from the surface. Thus, the inner phase is characterized by anaerobic, but viable, neoplastic cells. These surround the necrotic core, which contains few, if any, viable cells. Hence, there is a mass of anaerobic neoplastic cells which is far removed from the stroma and its blood supply and in which localization of chemical agents introduced into the blood stream will be poor. Further, the anaerobiasis of these cells appears to increase their radioresistance.[22]

The combination of these two effects suggests that for nuclides localized primarily in the stroma or in the areas surrounding but not perfectly permeating a lesion, the major portion of the ionizing radiation should be carried by particles of longer range. Optimally, their range should be just sufficient to blanket effectively all of the cell nuclei within the diseased volume. Destruction of a tumor growing edge alone would be insufficient to ensure against reinvasion by the viable, anaerobic tumor cells lying in the tumor core. Poor localization of chemical agents within the underlying layers of a tumor is, indeed, observed, and localization seems to occur primarily in the depolymerized ground substance[23] or in the stroma or macrophages surrounding the tumor.[2,6] While it has been suggested that ionic boron may be unique in its ability to localize within the nuclei of the growing edge,[4] the poor blood supply to the underlying layers of most tumors probably prevents effective localization within them.

In general it may be anticipated that many of the available mechanisms of localization will depend on the degree of inflammation of the lesion, and that the chemical agents employed will be present at highest concentration in the blood vessels and intercellular spaces of the lesion. Where localization is not uniform, particles with ranges of 2 or more cell diameters should prove advantageous since less of the total available dose will be expended in the blood and intercellular fluids and more in the nuclei and cytoplasm of the lesion cells. Particles with ranges of 40 to 100 μ (fission fragments) would blanket a relatively large volume of diseased cells and reduce the likelihood of survival of aberrant ones, even if the nuclide were not distributed uniformly. At the extreme, particles with ranges up to 10,000 μ (a 3-MeV β^-) should still be quite useful in organisms as large as humans. Even if tissues at this distance from the lesion surface were destroyed, the volume of normal tissue so encompassed would still be much smaller than that removed by surgical resection. The rapid decrease in dose with distance from the surface of the lesion[24] for such particles would severely limit the total dose to normal tissue, and the moderate LET would tend to result in uniform dose distribution within the lesion. This would help to ensure the total destruction of diseased cells even in regions far removed from the maximum nuclide concentration. Such considerations have undoubtedly been operative in the successful clinical use of such β-emitting nuclides as P^{32}, I^{131}, Ta^{182} and Au^{198}.

A considerable number of gamma-emitting nuclides have been employed for internal radiotherapy, most notably the members of the radium series. Photons originating in a lesion of small volume dissipate most of their energy in regions far removed from the lesion and afford only poor efficiency. However, the low-photon LET also results in a therapeutic situation similar to that obtained with well-localized, internally administered radionuclides. Thus, the average photon dose with a 1-cm lesion containing particles of radionuclide 100 μ or less distant from each other, is some tenfold greater than that at a point 1-cm from the surface of the lesion. The

photon energy released by most neutron capture reactions is much larger than the particulate energy released. In such cases the low absorption efficiency of the capture photons can be compensated by their greater energy. Such photon irradiation then proves a useful adjunct to particulate radiation.

The RBE of the various particles has been discussed and reviewed extensively,[25] and it does not appear feasible at present to calculate the dose of an ionizing particle required for production of a given biological effect. Nevertheless, for the particles important in neutron capture processes, the RBE as a function of LET appears to rise through a maximum and then declines with a total range of about 0.6 to 2. A preliminary choice of process could be based on the LET of the products, but, in view of the apparently limited RBE range, it appears that these differences among the various particles are not of primary therapeutic importance.

Energy Absorption

For any neutron capture process the total energy, E, released within an infinitesimal unit mass, dm, is given by

$$E_{dm} = (Q + E_n) N_a \rho^{-1} \tag{3}$$

where Q is the total nuclide disintegration energy and E_n the neutron kinetic energy. Q is much greater than E_n in the thermal or resonance regions, and the latter may be neglected. If we assume isotropic energy release in the laboratory coordinate system, we may define a quantity, $\overline{GE}_{dm}$, as the average energy released in dm and absorbed within a specified radius, r, of dm. Thus

$$\overline{GE}_{dm} = \overline{GQ}\, N_a \rho^{-1} = N_a \rho^{-1}(\overline{G_p Q_p} + \overline{G_\beta Q_\beta} + \overline{G_\gamma Q_\gamma} + \overline{G_n Q_n} + \overline{G_\nu Q_\nu}). \tag{4}$$

Here G is a form factor expressing the average fraction of the process energy absorbed within the specified radius. The five processes noted are the only ones of significance for $E_n < 10{,}000$ eV [i.e., heavy charged particle (p), electron (β), photon (γ), neutron (n) and neutrino (ν)].

Specific values for $\overline{G}$ may be fixed by defining the sphere of interest with a radius of 1 cm. For the neutrino at these distances, $\overline{G}_\nu = 0$. For charged particles greater than 1 emu, and for energies less than 3 MeV, maximum tissue penetrations are less than 1 cm and $\overline{G}_p = \overline{G}_\beta = 1$. The particulate energies characteristic of neutron capture processes are almost invariably less than 3 MeV. Neutron emission is significant only for the fission process, and even there it represents less than 2.5% of the total process energy. Values of $\overline{G}_n$ available from shielding experiments[26] and transport equations are of the order of 0.35.

$\overline{G}_\gamma$ may be obtained from the relationship

$$G_\gamma = B\, e^{-\mu R} \tag{5}$$

where μ is the photon macroscopic cross section and B the build-up factor. For values of R between 1 and 30 cm, and for values of E_γ between 0.1 and 10 MeV, B and μ vary slowly. Such values of R are those most likely to be encountered in dealing with human lesions, and values of E_γ in this range are characteristic of neutron capture processes. $\overline{G}_\gamma$ for such conditions lies between 0.017 and 0.035.[24]

Where the diffusion rate of the activated nuclide from dm is small compared to its decay rate, we may write

$$N_a = (nvt)\, N_A\, \sigma_a \tag{6}$$

and, combining Equations 4 and 6, we obtain the average dose, D, within the sphere of radius, R,

$$\overline{D}_R = \overline{GE}_{dm} = \overline{GQ}\,(nvt)\, N_A\, \sigma_a\, \rho^{-1}. \tag{7}$$

We may now define a parameter, $\overline{Y}$, normalized for density, concentration, and flux, by

$$\overline{Y} = \overline{GE}_{dm}\, \rho\, (nvt)^{-1}\, N_A^{-1} = \overline{GQ}\, \sigma_a. \tag{8}$$

This parameter may be regarded as the probability of energy absorption within 1 cm of an infinitesimal tissue mass of unit N_A, which is permeated by a neutron field of unit strength. Since $\overline{Y}$ includes the dose source functions it may be employed as a figure of merit for comparison of the various nuclides available for therapy. A number of these nuclides, with their $\overline{Y}$ values and data appropriate to their therapeutic evaluation, are listed in Table 1.

If the neutron field remains the same for each dm of less than 100 μg within the tissue mass, N_a will also remain uniform. Therefore, the average dose within the total mass may be computed by methods developed for the dosimetry of internal emitters.[24] For a tissue sphere of R $\geq$ 1 cm, this average dose may be given by Equation 7 with appropriate $\overline{G}$ values. For heavy particles and neutrinos, $\overline{G}_p$ and $\overline{G}_\nu$ remain 1 and 0, respectively. For the β-emitters listed in Table 1, G_β values range from 0.65 to 1.0 as an inverse function of particle energy. With increasing radius, these values rapidly approach 1.0 as a limit. For photons and neutrons, the new values are closely approximated by 0.75 R $\overline{G}_\gamma$ and 0.75 R $\overline{G}_n$ so that the average photon or neutron dose increases linearly with increasing radius. As $\overline{Q}_\gamma$ is usually much larger than $\overline{Q}_p + \overline{Q}_\beta$ the photon contribution to the total dose

is generally significant, and often dominant, despite low values of $\overline{G}_\gamma$. This photon effect increases with increasing size of the lesion.

As noted in the discussion of the neutron populations of the tissues, the field will not be completely uniform through lesions of finite size, as indicated in Equation 2. However, Σ_r is only 0.4 cm^{-1}, even for thermal neutrons, and the above simple approximations for average dose will not lead to very large errors for small lesions if an average value is employed for the neutron flux. Under these conditions the method outlined above yields useful approximations.

Available Processes

Using the above approximation for a sphere of unit radius, R, we obtain a value of $\overline{D}_R$ = 3800 eV/g for the average, normal tissue dose in a narrow beam of unit thermal neutron flux for "standard" wet tissue containing 0.5 ppm boron.[27,28] Because the nuclides of normal tissue evidence a "1/v" behavior, $\overline{D}_R$ will be at a maximum for thermal neutrons under narrow beam conditions, and the thermal value may be taken as a limiting one. At the other extreme the maximum $\overline{D}_R$ for an infinite beam occurs with epithermal neutrons, and the limiting value approaches 45,000 eV/g.[17] N_A for nontissue nuclides appears to be biochemically limited to about 4 x 10^{20} atoms/cm^3 since even the least toxic of compounds is lethal at this level.[29] To allow a useful therapeutic ratio of lesion dose to tissue dose, $\overline{Y}$ for a selected nuclide should, therefore, at least exceed 100 MeV-barn-cm^{-1}.

In Table 1, a number of nuclides which meet this criterion have been listed. Many elemental mixtures of high cross section, such as Kr, Pd, Ce and Os, have been omitted because of uncertainties in nuclide assignments. Data were obtained from standard sources[19,30-32] and augmented by private communications and estimates based on semi-empirical models. Unmeasured $\overline{Q}_\gamma$ values were estimated from mass differences,[33] and values for $\overline{G}_\gamma$ were taken as 0.028 cm^{-1} for the prompt $\overline{Q}_\gamma$ and 0.030 cm^{-1} for the delayed. $\overline{Q}_\beta$ values were computed assuming a Fermi distribution.[34] Sequential isomeric states are indicated by a hyphen, independent states by a semicolon. P indicates prompt processes. In some cases where activation integrals were not available, estimation by equation or from cross section curves proved feasible.[19,35,36] Values given for U^{233}, U^{235} and Pu^{239} are for fission process only, radiative capture having been neglected. Other transuranic nuclides, while attractive, are probably effectively unavailable. Values for σ_a were obtained by Breit-Wigner operation on given values of σ_t with available values of neutron widths. As no corrections were applied for resolution or Doppler broadening, these values of σ_a generally represent minimums. The value of $\overline{Y}$ listed is the sum of $\overline{Y}_p$, $\overline{Y}_\beta$ and $\overline{Y}_\gamma$, with $\overline{G}_p = \overline{G}_\beta$ taken as 1.0 for the maximum listed value of σ_a.

Table 1

EVALUATION OF NUCLIDES FOR NEUTRON CAPTURE THERAPY

Nuclide	Half-life, years	Abundance %	Decay process, products	$\overline{Q}_p$, MeV	$\overline{Q}_\gamma$ Prompt, MeV	$\overline{Q}_\gamma$ Delayed, MeV	σ_a^θ, barns	$\int_{0.07}^{\infty} \frac{\sigma_a dE}{E}$, barns	Resonance maximum, eV	Resonance σ_a, barns	$\overline{\nu}$ for σ_a maximum, MeV-cm^{-1}-barns	Half-life of products
He^3		00.00014	p,t	0.77	-	-	5,400	6,500	-	-	5,000	P;12.6y
Li^6		7.52	α,t	4.79	-	-	945	1,135	-	-	5,440	P;12.6y
B^{10}		18.8	a,Li	2.34	0.44	-	3,813	4,600	-	-	10,820	P
As^{75}		100	β^-,γ	1.04	7.32	0.74	5.4	35.3	47	890	1,125	26.4h
Se^{74}		0.87	γ,EC*	-	8.4	0.87	26.6		27.0	30,300	8,000	121d
Br^{79}		50.52	$\beta^\pm$,IT*,γ	0.80	7.92	0.40	10.4	140	35.6	3,000	3,100	4.38h-17.6m
Br^{81}		49.48	β^-,γ	0.14	7.76	2.65	3.1	163	102	800	350	36h
Sr^{87}		7.02	γ	-	11.10	-			3.56	1,100	345	P
Mo^{95}		15.70	γ	-	9.15	-	13.9		45.0	3,200	820	P
Mo^{96}		16.50	γ	-	6.75	-	1.2		133.2	890	170	P
Tc^{99}	2×10^5		β^-,γ	1.45	6.4	0.55	22.3		5.65	760	1,250	15.8s
Rh^{103}		100	IT,β^-,γ	1.02	6.82	0.11	152	625	1.257	5,000	6,100	4.4m-44s
Ag^{107}		51.35	EC,$\beta^\pm,\gamma$	0.63	7.27	0.01	45	112	16.6	1,220	1,020	2.3m
Ag^{109}		48.65	IT,β^-,γ	1.04	6.70	0.40	116	1,210	5.20	25,000	31,000	24s;253d
Cd^{110}		12.39	γ,IT	-	6.9	0.40	0.2		89	1,220	250	48.6m
Cd^{111}		12.75	γ	-	9.50	-			27.7	950	250	P
Cd^{112}		24.07	β^-,γ	0.19	6.6	0.27	0.03		67	510	200	P;5.1y
Cd^{113}		12.26	γ	-	9.05	-	20,000	30,000	0.178	65,400	16,600	P
Cd^{114}		28.86	β^-,γ	0.61	6.2	0.03	1.2		121	340	270	53h;43d
In^{113}		4.23	IT,β^-,γ	0.78	7.36	0.19	58	1,050	14.7	1,900	1,900	50d-72s
In^{115}		95.77	β^-,γ	1.44	6.59	-	207	3,300	1.457	30,600	49,700	13s;54m
Sn^{112}		0.96	EC,γ	-	8.14	0.49	1.3		96.5	3,200	780	
Sb^{121}		57.25	γ,IT,EC,β^-	0.57	6.8	0.63	6.8	162	6.24	2,270	1,770	3.5m-2.8d
Sb^{123}		42.75	β^-,γ	0.38	6.34	2.21	2.6	138	21.6	2,250	1,400	1.3m;21m;61d
Te^{123}		0.87	γ	-	9.35	-	410	12,000	2.334	44,000	11,500	P
I^{127}		100	β^-,γ	0.74	7.0	0.08	5.6	150	37.8	1,520	1,430	24.8m
Xe^{124}		0.096	γ,IT,EC	-	6.5	0.57	75		5.16	22,300	4,400	55s-18h
Xe^{129}		26.44	γ	-	9.20	-	45		9.47	7,650	2,000	P
Xe^{131}		21.18	γ	-	8.94	-	120		14.1	13,500	3,400	P
Ca^{133}		100	IT,β^-,γ	0.15	7.2	1.77	30	170	5.90	2,550	1,050	3.2h-2.1y
Ba^{135}		6.46	γ	-	9.5	-	5.8		82	790	210	P
Nd^{143}		12.17	γ	-	7.96	-	335		56	2,830	630	P
Nd^{145}		8.29	γ	-	7.49	-	60		43.1	6,100	1,300	P
Pm^{147}	2.6		β^-,γ	1.02	5.7	0.80	60		5.43	17,250	20,700	5.3d
Sm^{147}		15.07	γ	-	8.13	-	87		18.3	8,600	1,950	P
Sm^{149}		13.82	γ	-	7.97	-	61,000	74,500	0.097	122,000	27,000	P
Sm^{150}		7.47	β^-,γ	0.03	6.1	0.02			20	26,800	5,100	93y
Sm^{152}		26.63	β^-,γ	0.23	6.14	0.13	224	1,750	8.0	150,000	61,000	47h
Eu^{151}		47.77	EC,β^-,γ	0.50	6.5	0.47	7,700	12,000	0.461	22,200	15,500	9.2h
Eu^{153}		52.18	β^-,γ	0.19	6.3	1.37	420	950	2.456	6,200	2,500	16y
Gd^{155}		14.73	γ	-	8.41	-	70,000	88,000	2.64	9,000	20,700	P
Gd^{157}		15.68	γ	-	8.04	-	240,000	300,000	17.1	5,100	67,500	P
Tb^{159}		100	β^-,γ	0.21	6.1	1.19	22		3.35	1,000	415	72.3d
Dy^{161}		18.88	γ	-	8.3	-			3.69	4,200	1,200	P
Dy^{162}		25.53	γ	-	6.23	-			5.44	27,000	4,700	P
Dy^{163}		24.97	γ	-	7.8	-			16.18	4,900	1,070	P
Dy^{164}		28.18	IT,β^-,γ	0.44	6.37	0.11	2,610	3,150	146		2,000	1.25m-139.2m
Ho^{165}		100	β^-,γ	0.60	6.34	0.22	65		3.92	5,050	4,000	27.3h
Er^{167}		22.94	γ	-	8.0	-			0.47	12,000	2,700	P
Tm^{169}		100	β^-,γ	0.32	6.0	0.02	127		3.92	14,500	7,100	129d
Yb^{168}		0.135	γ,EC	-	6.7	0.63	11,000	20,000	8.05	171,000	35,300	31.8d
Lu^{176}		2.59	β^-,γ	0.14	7.7	0.02	4,000	10,000	0.142	14,000	5,000	6.8d
Hf^{177}		18.50	γ,IT	-	7.9	1.15	380		2.38	28,000	7,150	4.8s

Table 1 (Contd.)

Nuclide	Half-life, years	Abundance, %	Decay process, products	$\overline{Q}_p$, MeV	$\overline{Q}_\gamma$ Prompt, MeV	$\overline{Q}_\gamma$ Delayed, MeV	σ_a^θ, barns	$\int_{0.07}^{\infty} \frac{\sigma_a dE}{E}$, barns	Resonance maximum, eV	Resonance σ_a, barns	$\overline{Y}$ for σ_a maximum, MeV-cm^{-1}-barns	Half-life of products
Hf^{178}		27.1	γ,IT	-	6.16	0.38	75		7.80	20,300	3,700	19s
Hf^{179}		13.75	γ,IT	-	7.5	1.14	65		5.69	7,900	1,900	5.5h
Ta^{180}		0.0117	γ	-	7.8	-			0.433	13,500	3,000	P
Ta^{181}		99.99	IT,β^-,γ	0.14	6.07	1.45	21	600	4.28	13,000	4,600	16.5m-115d
W^{182}		26.41	γ,IT	-	6.32	0.16	20		21.2	7,100	1,300	5.5s
W^{183}		14.40	γ	-	7.43	-	11		27.1	4,000	830	P
W^{186}		28.41	β^-,γ	0.24	7.10	0.58	35	360	18.8	7,200	3,300	24.0h
Re^{185}		37.07	EC,β^-,γ	0.34	5.9	0.03	104	1,200	2.156	8,500	4,300	88.9h
Re^{187}		62.93	IT,β^-,γ	0.77	5.98	0.14	66	350	4.416	615	580	18.7m-16.7h
Ir^{191}		37.3	IT,β^-,γ	0.51	5.15	1.03	960	7,700	5.36	13,900	9,500	1.42m-74.4d
Ir^{193}		62.7	β^-,γ	0.69	5.6	0.31	130	1,500	1.303	9,200	7,900	19h
Pt^{195}		33.8	γ	-	7.99	-	27		11.9	5,600	1,250	P
Pt^{198}		7.19	β^-,γ	0.43	6.5	0.76	4.0		95.2	1,050	665	31m-3.14d
Au^{197}		100	β^-,γ	0.328	6.49	0.40	98.8	1,600	4.906	27,000	14,090	2.7d
Hg^{198}		10.02	γ,IT	-	6.88	0.53			23.3	6,600	1,375	42m
Hg^{199}		16.84	γ	-	8.04	-	2,500		33.5	7,650	1,700	P
Th^{232}		100	β^-,γ	0.47	5.0	0.42	7.3	95	23.6	2,050	1,300	22.4m-27d
U^{233}	1.6×10^5		fission	168	12	13	533	1,000	1.8	930	171,000	P_2fission prod.
U^{235}	7×10^8	0.71	fission	168	12	13	584	700	0.3	200	120,000	P_2fission prod.
Pu^{239}	24,000		fission	168	12	13	748	1,200	0.3	3,300	564,000	P_2fission prod.

*EC, electron capture
IT, internal transition

The fissionable nuclides appear most promising, possessing, as they do, the highest $\overline{Y}$ values coupled with prompt emission and particle ranges (40 to 60 μ) which seem well suited to therapy. While the fission products display a very wide range of decay constants, their total delayed energy output is less than 10% of the prompt energy. Chemical pretreatment[37] might decrease the fission product dose as discussed below, but in any case the effects arising from fission products would probably be small. For example, if we assume 6000 rads to be an adequate dose to the lesion, the delivery of such a dose to tissue containing U^{235} would produce only some 3×10^{-12} curies of Sr^{90} per gram of lesion.

Except for the He^3, Li^6 and B^{10} (n,α) reactions the remainder are of the (n, γ) type, with or without subsequent serial decay. In all, there are over 25 processes with $\overline{Y}$ values of the same order as Li^6 or greater and with half-lives of a few days or less. These appear to warrant consideration.

Along with these are a number of others whose use might be considered under favorable biochemical conditions. The naturally high concentration of I^{127} in the thyroid presents a unique case among the activatable nuclides. A dose of 6000 rads could be delivered to the thyroid within a few hours by activation of the I^{127} to I^{128} (half-life 25 minutes) with 38-eV neutrons. Total dose to neighboring tissues in the same interval would be quite small, and the whole-body dose would be negligible. I^{127} activation therapy of thyrotoxicosis and thyroid neoplasms would meet many of the

present objections to radioiodine injection therapy. The short half-life of I^{128} would give the therapist better control of dosage and would make possible a much smaller whole-body dose. The difficulties arising from reduced iodine uptake, which is characteristic of many thyroid lesions, could be circumvented by continuous treatment of the subject with normal iodine until a satisfactory level was reached. It might even be possible to treat lesions without uptake provided they still retained some of their natural iodine.

Neutron Sources

Neutron sources intended for capture therapy should provide a collimated beam with an energy appropriate to the selected nuclide and at a flux rate convenient for therapy. The neutron flux should also be relatively free from contamination by other ionizing radiation. Although precise requirements will be strongly dependent on the particular economic and therapeutic factors operative at each facility, some limiting estimates may be made from available data.

We may assume 6000 rads to be a reasonable total lesion dose and establish a minimum therapeutic ratio of lesion dose to normal tissue dose at 2. We may also take the dose to normal tissue, $\overline{D}_R$, for a narrow beam to be 3800 eV/g/n/cm^2 as before. Six thousand rads of this normal tissue contribution then correspond to a maximum integrated flux at the lesion of 5×10^{13} n/cm^2. Calculation of the maximum permissible flux density, using a value of 6000 rads for the maximum permissible skin dose, and a value of $\Sigma_r = 0.4\ cm^{-1}$ for flux decrement, yields a probable maximum permissible flux density of 10^{15} n/cm^2. At the other extreme, delivery of 6000 rads to a lesion 4 cm deep, containing 4×10^{20} atoms/g of Pu^{239}, would require an integrated flux density of 0.3-eV neutrons of less than 2×10^9 n/cm^2. The range of useful flux density may, thus, be estimated as 10^9 to 10^{15} n/cm^2.

In cases in which localization of the activatable nuclide in the lesion is relatively independent of time, the required flux rate will be determined primarily by the convenience of patient and therapist. A total irradiation time of 10^4 seconds (2.8 hours) is probably not excessive since anesthesia is unnecessary. This would require surface flux rates of 10^5 to 10^{11} n/cm^2-sec.

Clinical situations in which effective nuclide localization is obtained only for short spaces of time and poorly penetrating thermal neutrons are employed, as with current boron therapy, require high flux rates, and values as high as 3×10^9 n/cm^2-sec at the exterior body surface have been employed with only moderate success.(5)

In practice, the only contaminating radiation of consequence is that provided by photons of 0.05 MeV or over. A total photon dose of 600 rads

averaged over the E_γ range 0.1 to 10 MeV, corresponds to an energy flux of 2×10^{12} MeV-cm^{-2}. The removal cross section of such photons is about one-fifth that of slow neutrons so that a maximum surface neutron flux corresponding to a lesion dose of 6000 rads, the relative photon flux should be less than 0.01 MeV-cm^{-2} per n-cm^{-2}.

Following the lines of the discussion of the tissue neutron population little may be said about neutron energy requirements until the results of current computations are available, except that optimum values will lie between 0.1 and 1000 eV. For E_n values in this range, flux rate and gamma contamination requirements rule out available radioactive neutron (α,n) and (γ,n) sources for therapy, particularly when moderation losses are considered. The most attractive sources remaining are nuclear reactors and charged particle accelerators.

An extensive bibliography and review of reactor facilities for biological research has recently appeared and covers the majority of operating and proposed medical reactors.[38] Purely thermal flux rates of 10^9 n/cm^2-sec or higher appear to be readily realizable with "normal flux" reactors and are accompanied by gamma fluxes lower than the maximum specified above even when graphite or organic moderators are employed.[39] Carbon-containing moderators occasion a gamma flux arising from radiative neutron capture in C^{12}. Utilization of D or He^4 for moderation, coupled with Bi shields, would reduce this gamma flux still further but appears to be unnecessary.

So-called "pile spectrum" beams brought directly from reactor cores are available at flux rates up to 10^{10} n/cm^2-sec from relatively inexpensive reactors.[40,41] Reactors of higher core flux, such as the MTR, provide beams of over 5×10^{12} n/cm^2-sec with very low gamma contamination - generally less than 2×10^{-4} MeV-cm^{-2} per unit neutron flux.[42] Filtration of such beams with Li^6 provides high flux rates of approximately dE/E epithermal neutrons with no rise in gamma contamination. Crystal spectrometers are also employed with pile beams to provide monoenergetic neutron beams with energies to over 50 eV and flux rates up to 4×10^7 n/cm^2-sec with still lower gamma contributions.[42] Utilization of present ETR facilities would increase these values by factors of 5 or better. The coupling of intermediate spectrum reactors to crystal monochromators might also be suggested as a relatively low cost approach to even higher monoenergetic flux rates. Mechanical monochromators, while useful in the thermal region, are probably not feasible sources of monoenergetic epithermal neutrons.

Charged particle accelerators are excellent sources of fast neutrons at high flux rates and possess great versatility and excellent control characteristics. Nevertheless, present-day accelerators are not capable of producing moderated neutrons at flux rates approaching those from comparably

priced reactors, and their use would probably be considered only where shielding, operating ease and point source geometry conferred some special advantages.

For the production of monoenergetic epithermal neutrons, however, charged particle accelerators appear to be sources of choice. By employing processes of high yield, low threshold energies and low intrinsic photon contamination, such as certain (p,n) and (d,n) processes, monoenergetic neutrons can be obtained with the relatively inexpensive 2- and 3-MeV Van de Graaff or 1.75-MeV Cockroft-Walton accelerators.[20,43,44] Advantage may also be taken of the strong forward scattering of certain processes, such as $H(T,n)He^3$, and of close proximity of target to subject to obtain neutron fluxes requiring little further collimation.

Biochemical Aspects

In the therapeutic evaluation of a neutron capture system consideration must be given to its biochemical, as well as its physical characteristics. The chemical form of the nuclide chosen should localize in the lesions, be nontoxic to the subject and be stable to biochemical attack for a period at least equal to that required for irradiation.

The number of nuclide localization methods available for human lesions is, unfortunately, quite small and this lack undoubtedly constitutes the most serious weakness of neutron capture therapy. Localization of iodide ion in the thyroid has already been noted, and a number of compounds have been reported to localize in somatic tumors[45-48] although studies on many of these have not been extensively pursued. Analogs of these compounds could be prepared containing one or more of the nuclides of Table 1. Bromo, iodo, arseno and boronic acid derivatives would be particularly attractive because their chemistry is more familiar; but the metals, lanthanides and actnides, could also be coupled after having been immobilized in chelate structures as noted below. Synthesis of similar derivatives of the purines and pyrimidines might also prove feasible, combining chemostasis of neoplastic cells with neutron capture irradiation for concerted therapy.

The characteristics of the blood-brain barrier provide a rational avenue of approach to localization in brain tumors and one that has been extensively exploited for diagnosis and treatment.[2,5,49,50] Strong anions of low lipid solubility have provided the best localizing agents, and this aspect serves to direct the synthesis of appropriate agents.[9,12] Finally, direct injection of colloidally dispersed agents should serve well where a lesion is defined. Such mechanical localization methods are less attractive than those that allow localization without prior knowledge of the position and geometry of the lesion; but they could add the advantages of activation in situ to the present surgical implantation methods. In each case distinctive

color or fluorescence of the administered compound could be used to facilitate observation and control of the localization process. Use of heavy nuclides would add the possibility of radiographic observation.

The toxicity of any reagent may be classed as due either to its chemical reaction with some essential system in the organism or to its colligative behavior in disturbing the internal milieu. Chemical reactivity, colligative properties and neutron activation all are dependent solely on atomic, rather than mass, concentrations, and use of mass comparisons is not appropriate to capture therapy. We shall, therefore, express toxicities in atoms or molecules per unit mass to permit ready and meaningful comparison.

A third class of materials consists of those possessing negligible chemical activity and which occasion damage, if any, only through mechanical interference with normal processes. Such materials include the rare gases (He, Xe, etc.) and solids whose solution rate is infinitesimal (UC, BN, B_4C, U_3O_8, Ta, Pt, Ag, the various metal phthalocyanines, etc.). These solids may be administered as colloidal suspensions or as physically implanted beads or wires. Tissue fluids may be saturated with the rare gases, or the gas may be placed in cavities in balloons. Alternatively, they could also be administered as colloidal suspensions of their clathrate complexes. For each of these the maximum obtainable N_a will depend on mechanical, rather than chemical, factors, and values of the order of 4×10^{20} atoms/g or higher are easily attainable.

Of the nuclides in Table 1, Li^+, Cs^+, Br^-, and the borate anions are without toxic effect at 5×10^{17} atoms/g or higher and can be expected to remain relatively free of complexing and precipitation in normal tissue fluids. The alkali cations resemble Na^+ and K^+, and the halide anions Cl^-, too closely to permit very effective lesion localization except, perhaps, in neural tissues where K^+ concentration is high. Li^+, in particular, has not shown brain tumor localization even as great as that of the borates, very probably because of its positive charge and high mobility. Of the simple ionic forms of the potentially useful nuclides, the greatest promise appears to be offered by the borate anions in brain tumors.

Consideration may next be given to chemical forms in which the activatable nuclide is bound to some other chemically active structure. Many simple ions, such as I^-, are easily complexed with serum proteins and other tissue components in vivo, and the characteristics of such natural complexes may aid or hinder localization processes. Similar complexes may also be synthesized in vitro before injection, and the relative success of the various iodinated proteins and organics in localization studies attests to the potential of such methods.[2] Extension of such coupling to appropriate antibodies can result in a very high degree of localization specificity.[51] Unfortunately the methods of coupling ordinarily employed lead to complexes of only moderate stability in vivo. To be very successful, the strength of coupling

should be so great than an insignificant portion of the activatable nuclide is freed to the organism as a whole. This process involves both rate and equilibrium parameters for the various sensitive systems of the organism, and the prediction of the *in vivo* toxicity and localization behavior of a complex is not ordinarily possible from *in vitro* equilibrium data. Thus, despite very high association constants, protoporphyrin,[52] hematoporphyrin, alkylene diimino, and Pfeiffer[53,54] complexes of uranium have proved, in our hands, to be nearly as toxic as uranyl ion itself. Since the modes of death observed in mice were identical with those of uranyl poisoning, it may be inferred that the effective uranyl association constants of the sensitive systems of the organism were considerably higher than those of the chelates. Similarly lead ethylenediamine tetracetate has been reported to be nearly as toxic as lead ion despite the very high association constant of the chelate.[55]

While chelate complexes may not be sufficiently strong to serve as effective localizing agents for the very toxic activatable nuclides, they might prove useful with many of the less toxic systems. Further, pretreatment of the subject with such chelates[37] could decrease the biological half-life of undesired recoiling fission products or of the secondary products of a unique activated nuclide. The defined chemical characteristics of the latter system would probably permit a better choice of chelator than for the wide range of fission products.

To obtain compounds with association constants high enough completely to obviate release of the activatable nuclide to the organism, it appeared necessary to consider only chelates with very strong resonance stabilization components. It has been reported, for example, that the metal phthalocyanines[56] possess association constants too high to be measured by even the most sensitive radiotechniques.[57,58] We have confirmed these observations, resynthesizing many of the phthalocyanines previously reported and synthesizing other phythalocyanines of the I B, III B, VIII, lanthanide and actinide groups which are of interest for neutron capture therapy.[59] Many of these compounds have proved to possess negligible chemical toxicities, even when containing otherwise highly toxic nuclides.[49,50,59,60] Their chemical inertness suggests their use as chemical units for coupling immobilized nuclides to antibodies and other localization agents with minimum disturbance of their biochemical properties.

The methods developed for synthesis include fusion with phthalonitrile, metathesis with dilithium phthalocyanine, and reaction with urea and phthalamide. The compounds are deep blue or green solids with a strong purple color by reflected light. They contain one atom of metal per phthalocyanine residue and decompose *in vacuo* at 350 to 500°C to yield metal-free phthalocyanine as a sublimate. They are soluble in concentrated sulfuric and fluorosulfonic acids, from which they can be precipitated by dilution; however, some are slowly decomposed by this treatment. The lanthanide compounds are somewhat soluble in such organic solvents as dimethyl

formamide, and all are slightly soluble in quinoline, pyridine, chloronaphthalene, molten phthalonitrile and molten terphenyl. Dispersion as aqueous colloids has proved feasible.[59]

Because of the insolubilities of the compounds in aqueous media, it has been necessary to prepare solubilized derivatives for toxicity and localization tests. For use with brain tumors, sulfonated derivatives appear to meet the requirements imposed by the nature of the blood-brain barrier and considerations of toxicity. Many of them have been prepared readily, but with others it has been difficult to meet pharmaceutical standards of purity.

Development of systems employing metathesis with sulfonated phthalocyanine and fusion with sulfophthalic acids has aided greatly the preparation of many otherwise difficult compounds, but improvements in yield and purity are still being sought for others.

The alkali phthalocyanines hydrolyze rapidly in aqueous media. Only the lithium compounds hydrolyze, under certain conditions, at a rate compatible with therapeutic usage. In this case addition of the clathrate principle to the system holds promise of increasing the usefulness of these compounds. Thus, we have turned our efforts toward the synthesis of lithium phthalocyanine analogs with hindering groups or bridges extending over the central, planar ring so as to form a "cage" to inhibit attack and replacement. While theoretically feasible, this approach has thus far proved practically difficult, for the most part because the problems of synthesis of the requisite intermediates must first be solved. Similarly, organo-boron compounds which are nonhydrolyzable under physiological conditions have recently been reported.[1,12,13,61,62] The synthesis of sulfonated and other anionic, water soluble, derivatives of some of these compounds is currently under investigation, and certain of the borate esters have already proved effective in capture therapy of mouse tumors.[63,64]

Of the compounds prepared, that of greatest potential usefulness appears to be sulfonated uranyl phthalocyanine.[59] It has been obtained pharmaceutically pure only in low yield, but its pharmacological properties have been examined. Its minimum lethal dose in mice is well over 10^{18} molecules/g (2000 mg/kg), and such doses are without apparent effect on the health or breeding ability of the recipient mice or their offspring. Striking localization in brain tumors, with differential concentration ratios of 50 and over, has been achieved routinely, and the ratio of water- to benzene-solubility is in excess of 2×10^4. Location of the tumors is greatly facilitated by the deep blue color of the compound.

Because of the favorable pharmacological properties of the uranyl phthalocyanine, a number of other phthalocyanines have been prepared, both with activatable and nonactivatable nuclides, in the colloidal form and as

the water-soluble sulfonated analogs. A number of applications for such compounds suggest themselves: radiological contrast media, gamma and positron-emitting diagnostic aids, vital dyes for sequential light and electron microscopy of unfixed cells, carriers for activated or activatable nuclides for cell physiology studies or for selective inter- and intracellular irradiation, carriers for neutron coherent scattering studies, sources of carrier-free radionuclides, and carriers of fission products and other radionuclides for radiation-damage studies free of concomitant chemical toxicity problems. The slow excretion of the compounds from the system by way of bile duct and the intense colors suggest their use in physiological studies of the bile system. The colloidal forms of the unsulfonated compounds may prove useful in the neutron-capture irradiation of the organs and cavities where such compounds are normally localized or where they may be injected.

Summary

A broad survey has been made of processes and materials having potential usefulness for neutron capture therapy. Consideration has been given to the physical and chemical parameters of the processes involved in relation to the requirements imposed by the biological characteristics of lesions and of the organism as a whole. A number of promising systems are proposed; those which have been tested in the laboratory have given results in good agreement with theoretical expectations. It is concluded that optimum therapeutic results will be from the use of monoenergetic epithermal neutrons together with resonance capture and fissionable nuclides. The synthesis of resonance-stabilized compounds of activatable nuclides, in which the biochemical behavior is essentially independent of the key nuclide, is described, and such compounds promise to provide a number of useful therapeutic, diagnostic and research tools.

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