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Present Progress in Neutron Capture Therepy[1]

LEE E. FARR, M. D.[2]

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NEUTRON capture therapy may be defined as a therapeutic procedure primarily for control and destruction of malignancy. It is a procedure which utilizes a prompt, almost instantaneous, disintegration of the nucleus of a target element atom resulting from thermal or epithermal neutron capture. By this prompt nuclear disintegration, there are provided energetic particles of limited range thereby confining the effects of the reaction to the space immediately surrounding each capture element atom. It is highly desirable but not mandatory that the products of the disintegration be stable rather than radioactive nuclides. By selective distribution of the target atom within the region exposed to thermal neutrons, a high degree of selectivity may be obtained. Advantage is taken both of the large thermal neutron capture cross section of the selected target element in relation to the small thermal neutron capture cross section of normal tissue components and the large release of energy from the target element reaction compared to the smaller release of energy by the tissue component reactions. Complete transfer, that is about 95 per cent. of released energy of the target element capture reaction is accomplished within cellular dimensions.

From a consideration of thermal neutron capture cross section dimensions of those elements which by such reaction would disintegrate into energetic heavy particles, there are 3 elements meriting careful consideration, lithium 6, boron 10 and uranium 235. One can develop arguments favoring selection of any one of the three. After much consideration and some experience I have come to favor boron, a choice which experience has strengthened. In the subsequent discussions, I shall speak specifically of my experience with boron but in many instances the discussion is equally applicable to lithium or uranium. If one considers a large capture cross

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This research is supported by the U. S. Atomic Energy Commission.
[2] Medical Director Brookhaven National Laboratory Upton, L. I., New York U.S.A.

4001447

section element wherein the reaction will result in a release of an energetic beta particle, certain of the dimensions will change but the fundamental approach would not be significantly altered.

Neutron capture therapy, in this instance the utilization of thermal neutron capture by boron 10 for treatment of a brain tumor, glioblastoma multiforme, has been under investigation at Brookhaven National Laboratory since 1949. The present discussion will review in part the developments of the past seven years in this field. The idea of using what we have termed thermal neutron capture for treatment of cancer was first suggested in 1936 by Locher ([1]). It is a logical extension to medicine of physical reactions. The first experimental work on this problem appeared in 1940 when Kruger working at the Crocker Radiation Laboratory in Berkeley, California, published his observations on the effects of boron neutron capture in transplantable tumors ([2]). The same year Zahl and Cooper ([3, 4]) and Zahl, Cooper and Dunning ([5]) at Columbia reported similar observations. Further work in this promising field was postponed until after the war at which time reactors had been developed capable of providing the large numbers of neutrons so necessary for this particular study.

At Brookhaven, with the organization of the Medical Department in 1949, we turned our attention to this problem, of neutron utilization, limiting, however, the initial efforts to searches for a suitable carrier for boron since at that time the Brookhaven reactor was still under construction. During the few months immediately prior to completion of loading of the Brookhaven Reactor I first learned of Sweet's work on inorganic boron distribution between normal brain tissue and neoplastic tissue. A collaboration was organized which continued for a period of five years during which time two series of patients were treated. On February 15, 1951 the first patient treatment was carried out using the large Brookhaven Reactor with no resulting complications either to patient or the Reactor. The latter was subjected to stresses caused by very rapid change from no power to full power in order that critical timing demanded by physiological theory could be met. The effort entailed in this first treatment was very large. The borax used was synthesized from metallic boron 10 by Dr. H. L. Finston of the Chemistry Department at Brookhaven and a suitable synthesis had to be worked out for this. The large and very complex problems inherent in the demands made upon the reactor for a maximum thermal neutron flux attainment in a minimum time interval were worked out by the Reactor Department at Brookhaven under Dr. Lyle Borst. The Physics and Instrumentation problems, considerable at that time and still considerable, were and are being capably met by the Department of that name under Dr. J. B. H. Kuper. Almost the entire Medical Department contributed to the effort in one way or another while Dr. Sweet gave of his extensive neurosurgical skill for foil placement that proper measurements of intracranial neutron fluxes might be obtained. Despite the time which has since passed, the efforts we have made and I would say the presently deceptive smoothness with which the latest treatments have been run, it requires upwards of one hundred staff members at Brookhaven in various disciplines and with variegated skills to conduct these tests in such manner that each treatment may add significantly to our knowledge. The actual manipulation can be carried out by 15 to 20 people but if so done it can be only of a very routine nature. Some of the reasons for this are the basis of this discussion.

Let me briefly review the major hypotheses which are concerned in neutron capture therapy as it has been developed at Brookhaven. It is a therapeutic system so organized that by providing particles, e. g. neutrons, of low energy, penetration of a vital organ can be accomplished without significant tissue response to this component of the therapy.

4001448

Interamericana Acta Radiológica

These neutrons will pervade the space concerned promptly and in a predictable manner. Since neutrons can be measured fairly accurately, if the number entering the tissue volume be known, a reasonable approximation of distribution can be calculated. At the same time or immediately prior thereto it is also possible to load the neoplastic tissue of interest with a high cross section capture element, in this case boron, and this loading can be accomplished without significant toxicological risk and in particular without physiological impairment of tissue characteristics.

The interaction of thermal neutron and boron 10 is accompanied by a very significant release of energy, 2.3 M.E.V. divided between two heavy particles and 0.48 M.E.V. gamma ray in 92 per cent of the events. The total energy is transmitted entirely in 8 per cent of the events together by the lithium 7 atoms and alpha particles which result from the disintegration of the boron atom after thermal neutron capture. The distribution of the particle energy is sharply limited to approximately the dimensions of a sphere some 14 microns in diameter or roughly just slightly larger than one red cell diameter. Therefore the destructive effects of the reaction are confined by limiting the distribution either of thermal neutrons or of capture element atoms. In practice up to this time it appears more satisfactory to restrict the region which may be exposed to neutrons thereby gaining risk advantages as well as selectivity and to circumscribe the regional effects of the reaction by a knowledge of boron distribution. Free regional diffusion of neutrons has certain advantages in removing from the procedure geometric restrictions in relation to the tumor that otherwise would be very troublesome. By application of knowledge obtained, under ideal conditions a differential effect to destroy neoplastic tissue and preserve normal tissue can be utilized selectively to eliminate the neoplasm.

Sweet and Javid have shown that inorganic borate ion, from sodium tetraborate or borax, was for a time at least found in higher concentration in neoplasia than in normal tissue ([6, 7]). Since the ratio observed between neoplastic and tissue varied from 3 to 1 to 20 to 1, if thermal neutron saturation could be accomplished while these ratios obtained, the neoplasia could be eliminated ([8, 9]). This demanded on the basis of what we knew then, that thermal neutron exposure be carried out promptly after intravenous injection of the capture element so that treatment could be concluded within at least a forty-five minute interval. The first patient was given an intravenous dose of 1.59 grams of boron 10 as borax. This was administered in 50 seconds and subsequently the patient was irradiated for 17 minutes during which time a total of 0.44×10^{12} neutrons per square centimeter reached the presenting skin surface. Nine other patients were similarly treated and in five of the nine multiple treatments were given up to a maximum of four. The results have been reported in some detail ([10, 11, 12]). This effort established certain facts: the procedure was feasible, it was named neutron capture therapy; present practices left much to be desired for effectual therapy.

During the course of this work on the first few patients it became very apparent to those of us closest to it that despite what initially was believed to be a high flux of thermal neutrons was inadequate and would have to be increased. Further, the great technical problems of reactor operations required design and construction of a shutter device so that exposure could be made at will without change in the power level of reactor operations ([13]). Numerous pharmacological problems in regard to boron administration had also arisen although the major question of the safety of the procedure had been satisfactorily resolved. By this time it was also painfully evident that our efforts at instrumentation were a failure whereby we had hoped to obtain a measure of the integrated dose to the neoplastic tissue and the normal

4001449

tissue. All efforts to develop an alpha particle sensitive probe counter had failed. However it had been shown that a tissue equivalent plastic phantom gave results similar to those found intracranially when activation of gold foils was used as a measure of neutron flux. This made possible a more accurate mapping of isoflux lines to be expected in any given patient and confirmed the fact that for thermal neutrons a half value layer for intracranial tissue was on the average 1.9 centimeters ([14]).

Well over a year was required to design and construct a new facility in the reactor and during this period extensive observations were made on the pharmacology of boron and in particular the effectiveness of sugars in complexing boron at the pH of the blood. It was found that no sugar was significantly effective in this regard but some evidence was obtained that glucose might have some effect on the toxicity of boron if it were administered concurrently ([15, 16]). Pathological evaluation of tissues was slow and was far from conclusive since the exposure had been minimum in all cases.

The final patient of the first series of ten patients was treated in January 1953; and in April 1954 the first patient of the second series of nine patients was treated. The last patient in this series was treated in April 1955. For the second series of patients the new facility at the reactor provided a very significant increase in thermal neutron flux at the presenting skin surface, from 3×10^8 to 3×10^9. In the second series much greater uniformity of conditions was obtained by administration of the boron on a per kilogram body weight basis and its administration in 20 per cent glucose. Experimental work by Dr. Otho D. Easterday of Brookhaven had suggested that the original glycerineborate mixture enhanced the toxicity of administration. For this series Dr. E. E. Stickley and Dr. J. S. Robertson of Brookhaven designed and had made a local shield of lithium metal so that better protection could be provided for the proximal eye. It was with high confidence that the series was begun. This was shortly to change to concern as it became clearly apparent that the increase in neutron flux had brought to the procedure a new series of very vexing problems. These were to remain harassing throughout the period of treatment of our second series of patients and considerably retarded evaluation of therapeutic effects ([17]).

One of the most significant problems was posed by the development of a severe skin lesion over the port and adjacent facial areas. This lesion would appear about three weeks after treatment usually as a small point infection which would then spread with necrosis of the skin. Healing was incomplete and uncertain and all therapeutic maneuvers tried had only the slightest success. The cause of the lesion was not entirely clear and its distribution on the malar region of the face, proximal, did not help point out the solution.

The possibility of the capture reaction as the basic cause of this was considered but the distribution of the lesion threw some doubt on this explanation. A variety of procedures was tried with indeterminate effects. These procedures ranged from application of a pressure bandage over the skull, to tissue equivalent plastic shields placed in juxtaposition to the skin so that the presumed neutron build-up in transfer from air to more solid media would occur in the plastic rather than the skin and at the same time protect the skin from nitrogen, proton reaction of air. Work by Bond, Easterday, Stickley, Robertson, Lippincott and Farr on neutron effects on the skin of the pig before and after administration of boron showed that the capture reaction was likely the most significant factor and very possibly the only factor ([18 a, 18 b, 18 c]). This skin lesion was a serious deterrent to progress in patients for some period of time. Finally in January 1957 following the development of equipment deemed capable of permitting, at a distance, controlled

4001450

rates of injection into the internal carotid artery, irradiation of the third series of patientes was begun. Thus far in six patients it appears that finally it has been possible to make a satisfactory prediction of the time of skin saturation and thereby to carry out high flux treatments without development of any skin lesions ([19]). Until final histological examination can be carried out, however, with this altered procedure we cannot be certain of the maintenance of the same intracranial distribution characteristics as previously of the capture element. The new Brookhaven Medical Research Reactor which is expected to begin operations this fall will be of great value in furthering these investigations ([20]).

This concludes a brief running chronological account of the procedure in which changes in method were required to maintain the development of the procedure. However one of the two main questions at issue is: Were the malignancies adversely affected by the treatment given? I believe the answer to this is affirmative though evidence is not unequivocal and must rest at least in part upon concomitant and as yet unreported studies of control of an experimental transpantable invasive methyl cholanthrene generated tumor of the central nervous system of mice. The second main question at issue is: Has any damage occurred to the normal regions of the central nervous system adjacent to or more distant from the neoplastic invasion? Here the answer must be a very tentative No. It is tentative not because the data to date are equivocal but because we believe we have in progress a comprehensive observational study which will permit us definitely to answer this question but until these scrutinies are complete we have only meager information upon which to base our conclusions ([21]).

Clinically in every patient we obtained some evidence of retardation of tumor growth following treatment. In some instances this was manifested by improvement of function in the patient, in others it was a pause in the rate of progression of deterioration, but a measurable and noticeable pause. To the question was life prolonged, we can give no accurate answer. Probably so but this cannot be clearly demonstrated. This will be made clearer by a comparison of survival periods

TABLE I

DATA SUMMARY ON PATIENTS RECEIVING NEUTRON CAPTURE THERAPY FOR GLIOBLASTOMA MULTIFORME

	Series 1 (10 patients)			Series 2 (9 patients)		
	Average	Median	Range	Average	Median	Range
Boron-10 dose Mg/Kg body weight	25	26	16-43	42	42	32-50
Thermal Neutron Exposure (Skin Surface) x 10^{12}	2.15	1.50	44-5.31	3.30	3.38	2.34-6.09
Days between first surgery & radiation	134	90	32-602	48*	44*	14-90
Days survival after first radiation	108	97	43-185	186	147	93-337

* 8 Patients only — ninth patient first operated on 1359 days before radiation.
— ninth patient survival 121 days postradiation.

400 451

of the patients in series one and two ([22, 23]).

These results can be taken as the basis of a discussion of some of the successes achieved and the large number of problems to be solved many of which are the outgrowth of the work itself. If one compares these data for average boron 10 dose, average neutron exposure to presenting skin surface and average survival period after radiation, it is seen that with an increase in boron administered and with an increase in thermal neutron exposure, average survival increased in duration. This at least suggests that by such procedures nothing inimical to life has been done. There are also no data not in agreement with our hypothesis that as yet the dose administered is inadequate. The difficulty of evaluation of a small series of patients like this epitomizes the problem of evaluation of cancer therapy. Survival can be measured only from the time a given therapeutic procedure was administered and this is an arbitrary and chance date in the natural history of the disease. We cannot accurately date the onset of this disease nor having established the diagnosis can we predict what the life expectancy of any given individual may be. These difficulties with a rapidly progressing disease like glioblastoma multiforme are magnified greatly with other neoplastic conditions particularly those in which therapy may be partially successful. It is imperative that knowledge be extended regarding the natural history of glioblastoma multiforme and that every effort be made to develop a basis for prediction of individual longevity. While I have spoken in terms of glioblastoma multiforme, the necessity for this kind of information is paramount for all highly invasive neoplastic lesions of the central nervous system which might be suitable for this therapeutic approach. To date our best evidence suggests that the physiological criteria which we are requiring are related more closely to what may be termed invasive qualities of a tumor than to specific cell type. Using this criteria I can say that our patients have had a high degree of uniformity. This can be a conclusion arrived at only by a post mortem study since the vagaries of cell structure in these tumors are so great that no single biopsy specimen can be expected to reveal all the necessary pertinent qualities which must go into such an evaluation. The problem then of selection of the patient to be treated can not today be placed upon a truly systematic basis but must remain up to the best judgment of the physicians who are concerned with the study. In this circunstance, the fact that most clearcut answers can he obtained most rapidly from those patients who have the most invasive tumors suggests that the best selection will also be the most rigid selection. Thereby greater validity is given to the results obtained. Other aspects of the patient selection problem are of interest but not germane to this review. Some differing views have in part been expressed by Sweet and Locksley ([24, 25]).

Perhaps the most vexing problem which we face is the estimation of radiation dose delivered to the tumor. Since our efforts to develop an alpha sensitive probe counter have been unavailing, we find ourselves in the position of being unable to give any accurate estimate of dose. Although at various times authors have computed dosages ([26, 27]), these are all based on assumptions not necessarily all completely proved ([28]). We are, as I indicated before, able to determine with sufficient accuracy the neutron exposure of each and region of the tumor. This data can be obtained as the total regional exposure. However, to calculate dose we must also have precise data on boron 10 concentration of the tumor and in this we are completely deficient, though efforts to remedy this have been made ([26, 29]). We must have the boron 10 concentration for each region of the tumor since the neutron flux will vary with distance from the portal. In addition to this we know that boron concentration is changing with time and that any over-all estimate of concentration change with time will be

4001452

inadequate even if we could arrive at such a figure. Under operative conditions one can not be assured of maintained physiological intactness of the systems involved nor can one by naked eye or by any device now available separate pure neoplastic masses from pure normal tissue masses when one is dealing with glioblastoma multiforme. It must be recalled that we are dealing with the tumor cell by cell. The hypothesis I believe most likely, requires an individual cellular difference which is operative no matter how small a neoplasia may be or what its relations may be to adjacent normal tissue. It would appear to be a problem which is incapable of solution by attacks as made previously and therefore must be approached by an entirely different technique. Since there is no true experimental counterpart in animals it means that all of this exploratory work must be done within the framework of best possible therapy for the individual patient. This restricts the number of approaches that can be used but with this type of restriction one certainly can have no quarrel. It raises, however, a serious question in my mind and that is whether any useful purpose is served by making calculations based upon a number of unsupported assumptions. As a result of such calculations there can arise a tyranny of numbers, the compulsive obsession of which by the experimenter may well blind him to the necessity of a truly open mind in observation of obtainable and reproductible data. That is, I believe it may be of valuc to engage in such computations when we have some security in the components of the equations but until that time I believe we must rely upon hypothese and experimental empiricism to outline the parameters of productive experimental endeavor.

A correlary to this discussion is study of the pharmacological effects of the compound used. We have found that it is necessary for us to carry out experimental observations on the reinforcement or attentuation of action of each drug used concomitantly with treatment that we might not unwittingly exaggerate untoward effects and thereby possibly defeat our own objectives. The whole question of pharmacology of boron has been reopened since we have demonstrated that very large doses of boron may be given with safety though not without provocation of effects. It has been shown in our studies that slight changes in inorganic salts may be accompanied by profound changes in toxicological properties. Morphine has its action reinforced by boron which in turn has its toxicology enhanced by morphine whereas chlorpromazine appears to antagonize some of the effects of boron while its own action remains apparently unaffected. The results of sudden loading of the central nervous system with boron have not previously been important but now become of prime interest and in this area we found no satisfactory existing information. The effect of glucose in reducing the toxicity of boron and the fact that this effect was found by Easterday to go through a maximum point becomes of vital importance under the conditions of operation of this study. The determination of the blood-brain barrier becomes a prime object of attack and to all these one must add the effects of radiation thereupon both immediate and subsequent. The development of new organic compounds of boron one is inclined to believe will ultimately provide a better boron carrier than the sodium pentaborate developed in the Medical Department at Brookhaven and now being used, but even at the present moment we are completely in ignorance of what are the reasons for differences in pharmacological actions between sodium tetraborate, borax, and sodium pentaborate an empirical derivation of borax. At the moment the pentaborate is by far the best compounl found for practical use and it is being used for the first time in our current observations in series three. Despite prolonged study of pentaborate there is much more we would like to know of its effects. A similar discussion can be made for each

4001453

of the other prime capture elements of use in this treatment.

Data on the kinetics of distribution of capture element compounds are some of the most important data needed. Unfortunately, there is no radioactive isotope of boron or of oxygen which would permit tracing of movement of the borate ion in a biological system. Chemical analysis, which in itself is not too satisfactory for boron, suffers from a severe restriction in the time required to take samples and the physical measures necessary for the taking of samples. It is apparent that we are dealing with transfers between very complex multicompartment systems responsive in part to elusive and poorly documented influences. Under these circumstances we can only intensify investigations on the kinetics of distribution of a number of different compounds that can readily be traced and hope that data derived from such studies will be applicable. In the search for precise information wherein we seek for knowledge regarding sequential events cell by cell, we may be betrayed by placing too much confidence in data which must be explained by analogy. It is of importance to know whether or not intracellular transfer of boron involves specific transport systems, whether or not intracellular boron is uniformly distributed or is concentrated within certain intracellular structures and above all what are the relationships between boron entering a cell and displacement of some other as yet unknown ion that ionic equilibrium may be maintained. We have studied data on the kinetics of distribution of sodium, potassium, chlorine, manganese and tritium at some length as well as the behavior of larger labeled molecular aggregates like proteins to help us disern the principles which may govern the movement of boron. Since we are concerned with boron distribution throughout all parts of the body we cannot neglect tissues-other than the central nervous system. The peculiarities of this system such as the blood-brain barrier phenomena have not added to the ease of interpretation. As we may become concerned with organic carriers of boron it is necessary to have information on the kinetics of distribution of these compounds and their similarities and differences to the behavior of inorganic ions.

Closely related to, if not actually a part of the study of kinetics of distribution is a need for better knowledge of cellular physiology of the organ of interest. While in general the circulatory relationship to function of a given organ is known, usually there is ignorance of differences in function or rates of function of varying parts of a single organ. Evidence is coming to light that one cannot blindly assume a uniformity within an organ but that time relationships become important in determining whether or not uniformity may exist at the moment of critical observation. Better knowledge of cellular physiology will also provide a sounder basis for seeking differential phenomena between injured and normal cells and treated and normal cells. This may be of great significance in helping to evaluate early the effects of any given course of action. Anatomy in histological detail as well as complete knowledge regarding circulatory pathways becomes of great significance indeed. The responce of all functional systems studied to specific drugs, hormones or chemical compounds used becomes a necessary part of physiological knowledge.

Upon one additional area of knowledge I will touch lightly. This is the usefulness of epithermal neutrons in this procedure. We need to have better means for producing monoenergetic beams of neutrons in requisite fluxes; to know the mechanisms of energy transfer by epithermal neutrons to biological systems; the feasibility of using tissue to thermalize epithermal neutrons. I do not mean to imply by these remarks that our knowledge of thermal neutrons in relation to biological systems is complete but only our knowledge in relation to epithermal neutrons is woefully incomplete. Other problems

4001454

of instrumentation and dosimetry may be mentioned for the sake of completeness. Until additional instrumentation can enable us to make meaningful measurements at the time procedures are carried out we must rely on accumulation of experience to evaluate certain procedural changes. The Brookhaven Medical Research Reactor is designed to further these studies also.

In conclusion, I believe that a study of neutron capture therapy is promising as a procedure which might result in a better control of certain neoplastic disease not now susceptible to effective treatment; the scientific problems associated with this practical application are of such importance that there should be widespread encouragement of study in this field; the area of knowledge in which additional data are sought is so extensive that no single institution or small group of institutions can hope to provide adequate coverage of the field; solutions of the problems require the efforts of the scientific fraternity as a whole.

SUMMARY

The author presents a study of neutron capture therapy, which he defines as a therapeutic procedure primarily for control and destruction of malignancy.

He reviews the developments of the past seven years in this field, and he gives a report of the research work carried out at the Brookhaven National Laboratory, with a discussion of the results obtained.

RESUMEN

El autor presenta un estudio del procedimiento de captura del neutrón, que define como un método terapéutico empleado, primordialmente, para el control y la destrucción de la malignidad.

Pasa a los adelantos alcanzados en este campo, en los últimos siete años, y da un informe de las investigaciones realizadas en el Brookhaven National Laboratory, con una discusión de los resultados obtenidos.

RESUMO

O autor apresenta um estudo do procedimento de captura do neutrón, que define como un método terapêutico empregado primordialmente, para o controle e a destruçao da malignidade.

Passa revista aos adiantos alcançados neste campo nos últimos sete anos e da um informe das investigacões realizadas no Brookhaven National Laboratory, com uma discussão dos resultados obtidos.

RÉSUMÉ

L'auteur fait une étude du procédé de capture du neutron, qu'il définit comme une méthode térapeuthique employée, primordialement, pour le contrôle et la destruction de la malignité.

Il passe en revue les progrès atteints dans ce domaine pendant les sept dernières années et il publie un compte-rendu des investigations réalisées au Brookhaven National Laboratory avec une discussion des résultats obtenus.

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4001455

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Lee E. Farr, M. D.
Brookhaven National Laboratory
Upton, L. I., New York, U.S.A.

COMPAÑÍA IMPRESORA ARGENTINA S. A.
Alsina 2049 – Buenos Aires

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