

MEMORANDUM TO BOARD OF MEDICAL CONSULTANTS
ON MEDICAL PROGRAM

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By: Dr. Marshall Bruer

Whether we care to admit it to our candidates or not, the basic idea which underlies the Medical Division of ORINS is the therapy of cancer with radioactive substance. This is the purpose for which the money was appropriated and our attempts to "interpret" the words "study of cancer" is in itself an admission of a fundamental criticism of the program. This criticism has been voiced by each of the candidates we have interviewed and is the first thought of most persons when they hear of the proposed program. It is based upon two well known facts. First, cancer research holds less promise of significant results than any other single subject for study. Second, radioactive substances have not yielded the cure-all properties widely predicted for them.

No one doubts the potentially unlimited usefulness of the wide variety of radioactive substances yet uninvestigated, nor does the field of cancer research lack profitable approaches. We have emphasized a generalization on "opportunities unlimited" but when asked the specific question on how to combine the two restrictions, radioactivity and cancer, the answers are not forthcoming in a rush. In trying to clarify my own answers to our candidates' questions I have written out the following impressions. Since it embodies my own recommendations on the cyclotron-betatron question, I include the entire note as a memorandum to the Board.

In discussing any proposal for cancer research a number of generalizations should be kept in mind. The first concerns the ultimate biological action being sought; second, some general characteristics of cancer; and third, the possibilities of a new radioactivity approach.

I. The basic purpose of cancer therapy is to kill cancer cells without killing normal cells. There are limits to this idea. First, it is not necessary that only cancer cells be killed. A certain number of normal cells may be killed with impunity and this number is a function of both temporal and spatial variables. To a certain extent the variables are known; e. g., many liver cells may be killed in a unit of time but only few nerve cells; in some areas skin may be damaged extensively with reasonable probability of adequate repair, but sense organs and gonads usually show irreversible damage.

A second limitation is that each dying cell imposes an additional load upon the body and there are spatial and temporal limits to the number of dead cells that can be disposed of. The toxicity of necrotic substance and the energy requirements for repair each limit the destruction the body is capable of enduring in a unit of time.

There are two basic approaches to the problem of killing cancer cells. One is by removing the cells from the body, the surgical approach. The second is by destroying the cells within the body, the pharmacological approach. Included as a special case - special only by virtue of its recent history - is the use of radioactive pharmacological substance.

The surgical approach has limitations. Surgery is a form of trauma and carries a danger even in healthy bodies. Further it is accompanied by anesthesia which is in itself a morbid state with some danger. The surgeon is limited to the removal of a limited number

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of discrete masses of tissue. For example, Steiner, P. E. et al, (Am. Jr. Path. 24; 947-961, Sept. 1948) describe the three factors apparent in 5 year survivals after gastric carcinoma. By far the most important was sharp circumscription of the tumor.

These masses even when discrete must often be removed from positions ill suited for dissection and invariably involve the removal of normal tissue. The necessity for more radical dissection is becoming more and more apparent. Eker (Carcinoma Ventriculi, Acta Chir. Scandinav. 88; 556-572, 1943) demonstrated that in gastric carcinoma malignant cells could be found as microscopic extensions five centimeters beyond the apparent (surgical) margin of the tumor mass. But more radical dissection imposes greater hazards in removal and decreases rather than increases the usefulness of the surgical approach.

The pharmacological approach to cancer therapy has been notably unsuccessful. Scepticism has reached the point where it is possible for new ideas to be discarded even before adequate clinical trial. The problems revolve endlessly around the duality of adequacy and toxicity and centers on the fact that no known drug will automatically select a cancer cell from a group of normal cells.

The special case of radioactive therapy has butted against the limitations of both of the basic approaches. The two well known radioactive substances used in therapy, P^{32} and I^{131} have not turned out well. After thorough study Reinhard and co-authors (J. Lab. Clin. Med. 31; 107, 1946) have issued a completely discouraging report on the use of phosphorus. Doan et al (Jr. Lab. Clin. Med.) confirm the Reinhard study in another extensive series and conclude that with few exceptions isotope therapy has no significant effect on the course of the disease. Reinhard's summary to me following our last meeting was that he intended to forget the whole P^{32} problem as an interesting but useless interlude in the therapy of Leukemias. The remarkable isolation of iodine by thyroid tissue has created a flurry of medical propaganda in thyroid carcinoma therapy but mostly by persons who have not used it. As long ago as 1941 Hamilton (Jr. Applied Physiol. 12; 260, 1941) showed radioautographs of thyroid cancer cells not picking up radioactive iodine. Again in 1942 Hamilton (Radiol. 39; 541-572, 1942) stated that thyroid carcinoma had no ability to store radioactive iodine. LeBlond et al (Jr. Biol. Chem. 162; 275-285, 1946) showed that even thyroid adenomas were much less active in storing I^{131} than other tissues. Keston and Company (Science 95; 362-363, 1942 and Am. Surg. 119; 668-689, 1944) showed that in two of three patients skeletal metastases did not pick up any I^{131} and in the other case there was a minimal pickup of iodine in one well differentiated metastatic spot. Rawson and others (Western Jr. Surg. Obs., Gyn. 56; 82-95, 1948) state that of 12 thyroid malignancies none showed more than a minimal pickup of I^{131} - the selectivity of iodine by metastases was spotty and unreliable. Means (West. Jr. Surg. Obs. Gyn. 56; 65-71, 1948) emphasizes the unreliability of Iodine in Thyroid Carcinoma by discussing the use of antithyroids to increase iodine collection by malignant tissue so that therapeutic doses will be taken up.

The older methods of radiation therapy - X-ray and radium - each have their own disadvantages. X-ray is limited by the same factors which limit the surgical approach; those of localization of tumor masses, and of concentration of activity in these masses. Taking the place of surgical trauma there is often an even more serious radiation trauma to overlying tissues. Even though not strictly true, the surgeon's statement that "x-ray never cured a cancer" illustrates the inadequacy of X-ray therapy.

Radium therapy has historical importance, but it must be placed in the tumor mass which must be in favorable position, must be circumscribed, must be highly sensitive to useable

doses and must eventually be removed. These limitations are again those of the surgical approach with the added danger of radiation.

An improvement on radium might be found in the use of radioactive gold. Here the improvement rests upon characteristics which allow a more accurate deposition of an insoluble salt of favorable half-life throughout the tumor. Many of the disadvantages of the surgical approach remain, but for the second time, (iodine was first even though it is petering out) some advantages are appearing that open up a new approach to the problem of cancer therapy. Before this is discussed the general situation in cancer should be reviewed.

II. If the importance of a disease can be described in terms of the number of persons it kills, then cancer is the second most important disease. On the basis of the entire population, male and female, all ages, if all cancers of skin are given an index of numerical importance of 100 then the relative importance of a group of other cancers is roughly as follows: (Adapted from Public Health Reports 59:74, 1944)

Skin	100	Rectum	41	Lip	18	Mouth	9	Testis	4
Breast	95	Prostate	29	Ovary	18	Larynx	9	Vagina	4
Uterus	86	Bladder	26	Pancreas	12	Kidney	9	(Leukemia	-1)
Stomach	71	Lung	21	Bone	11	Tongue	7		
Intestine	53	Liver	19	Esophagus	10	Brain	7		

The three most important cancers are strategically placed for surgery. Cures are reasonably frequent and the problem is probably best approached through the training of the public and physicians in early diagnosis and in the training of surgeons in adequate removal.

Of the next three, cancers of intestine and rectum have a reasonable probability of being cured by good surgery following reasonably early diagnosis. For example, in a recent study of cancer of the colon, Joyce (West. Jr. Surg. 56: 110-119, 1948) finds that the cancers are recognized early, two thirds before 10 weeks have passed; they are located in areas well suited to dissection since most are in the right colon, sigmoid or recto-sigmoid; the surgical mortality can be as low as 12% and there are a significant number of long term cures. Gastric cancer, however, shows an entirely different picture.

G. T. Paek in a discussion of a paper by Glenn (Ann. Surg. 113:631, 1941) estimates that of 100 patients admitted to a hospital for gastric carcinoma, about 25 are suitable for resection. Of these 25 resections 5 - 10 will die from the operation and of the 15 - 20 survivors only 2 or 3 will be alive five years later.

In the recent series of Maimon and Falmer (SGO 83:480-484, 1946) in only three fourths of 576 patients admitted to the University of Chicago Clinics for Gastric Carcinoma was laparotomy advised. Of 466 patients who wanted to follow the advice, laparotomy was performed in about 84%, a fifth of these operations were mere explorations, palliative procedures alone were possible in another fifth. Resection was considered possible in 389 patients (including many desperate risks) of which only 150 survived the operation. Even on exploratory procedures alone there was a 14% operative mortality. Other series quoted, show similar results. Hausen (Denmark) in reviewing 1547 gastric carcinomas found a fifth resectable and a 42% resection mortality. Walters Gray and Priestly (Arch. Surg. 46:939 - 937, 1943) in 10,890 cases found laparotomy possible in 57% but did only 26% resections and hence had a lower resection mortality of 16%.

The story of five year cures is even more discouraging. Schindler (SGO 83:453-461, 1946) reports no five year cures in 56 carefully studied patients but finds six three year

cures in the surgically favorable gross types I and II and one three year cure is the surgically unfavorable type III. The conclusion of Livingston and Pack (End Results In Treatment of Gastric Cancer, New York, P. Hoeber, Inc. 1939) is worth quoting. "Gastric surgery does not now, nor is it likely in the future, to prove a satisfactory answer for more than the smallest number of patients."

In the case of the relatively less important cancers a similar picture can be described. In some, larynx, bone, kidney, lip and tongue cancer, cures seem possible by surgery; but in the case of lung, liver, esophagus, brain, etc. and certainly in the case of the least important (by numbers) leukemia, the story of therapy is one of constant failure.

The large sums of money now being spent on cancer research are rightly funneled to basic research on the general problem of growth and to investigations on cytological biochemistry and physiology. However, some search should continue for therapeutic measures since, historically, therapeutic accidents have occasionally preceded an understanding of the nature of a disease. The question thus arises, what new approach to cancer therapy is opened by the availability of radioactive substances?

III. The entire problem of cancer therapy is seen to revolve around two procedures. One is the localization of cancer cells, the other is either the concentration of lethal substance within the cell or the removal of the cell. It is known that any rapidly moving sub-atomic particle (or sub particle) when introduced into the cellular matrix of atoms in sufficient concentration will kill the cell. It is also known that (as yet) there is no way for these particles to distinguish between a cancer and a normal cell. However, with 750 nuclides to choose from, the problems of localization and concentration have been opened to a wide range of substances with a wide range of specific activities in many chemical combinations with a wide range of radiation intensities.

To decide which isotopes to investigate is a difficult problem. To summarize Hahn's complete discussion: (Ann. Int. Med., March 1948) On the basis of the following criteria, i. e. half life 2 -10 days, known biological and chemical behavior, reasonable radiation spectrum, preferential tissue deposition, toxicity and cost, only about 6 to 10 isotopes show promise. Unfortunately Hahn's 2-10 day limits fall at a low point on the half-life frequency distribution curve. (Nucleonics May 1948 Part I page 26-27) The most frequent half lives fall in the 10 minutes to 1 day range which are within the decay limits of an Oak Ridge Program.

If the half life requirements are cut down to the range 12 hours to 3 days about 67 new isotopes are added; if cut down to the range 1 to 12 hours another 90 or so are added; by using the 10 minute to 1 hour range 100 more are added. Unsuitable radiation spectra causes many of these additions to be discarded, unknown biological behavior seriously reduces the list. However the elements need not be used as elements. Since the biological behavior can be controlled by chemical combination with other elements, the list of possibly useful substances is increased tremendously. A repetition of Hahn's survey on an additional 250 isotopes is necessary. Since the ORINS program will be one of the few to which short lived substances are available such a survey would seem to fall within the scope of the medical division of ORINS.

Even this discussion is too general to answer the big question in the minds of our candidates. To illustrate one specific method in which radioactive isotopes might profitably be used, the problem of gastric carcinoma may again be brought up.

There will be roughly 36,000 deaths from gastric carcinoma this year, with an increasing population age this will increase about 40 - 50,000 deaths per year in 1960. Hence, the

disease is numerically important. Cures are rare; hence, an isotope program can do no harm.

The disease can be diagnosed with accuracy. Maimon and Palmer (SGO 83:572-574) found a correct diagnosis by gastroscopy in 80-90% of cases and a correct diagnosis by X-ray in over 90% of cases. Inconclusive diagnoses may occur but incorrect diagnoses are rare if reasonable care is taken. With ease of diagnosis the question of defining a homogenous group for study is approachable.

The disease is sufficiently rapid to allow for a reasonable test within a period of a few years. The duration of symptoms from start to positive diagnosis in three studies was as follows:

	MAIMON AND PALMER	WALTERS GRAY PRIESTLY	FAGED AND LASSEN (DENMARK)
Less than 3 months	26%	18%	40%
3-6 months	21%	19%	24%

Since most of these were already too late for surgical cure it is evident that the disease is one of rapid progression. There is little evidence that mass testing by X-ray or further education of the dyspeptic public will allow gastric carcinoma to be recognized much earlier.

One other characteristic of gastric carcinoma makes it available for an isotopes study. Over 25 clinical units of free acid was present in over a third of the Maimon Palmer series. Bockus (Gastroenterology Vol. I, Saunders, N. Y. 1946) points out that the well known hypochlorhydria of gastric carcinoma is for free acid without histamine. Most gastric carcinomas show considerable combined acid; about a quarter of cases have a combined acid above normal.

Manery and Hoegge (Am. Jr. Physiol. 134: 83-93, 1941) demonstrated a rapid penetration of Cl^{38} into rabbit gastric mucosa. Eisenmann, et al, (Jr. Biol. Chem. 140: XXXV, 1941) showed that radioactive chlorine in an obstructed stomach or in the isolated gastric pouch of a dog was transferred back across the stomach wall to only a slight extent. Brunschewig and Schnitz (Proc. Soc. Exp. Biol. and Med. 43: 438-441, 1940) injected Cl^{38} I. V. and were able to demonstrate considerable radioactivity for from 10 to 130 minutes in a gastric pouch stimulated with lean meat.

In an 18 hour starved human post operative cholecystectomy case they injected 400 mg. Cl^{38} (as $LiCl$) I. V. and Histamine 1 mg. S. Q. and observed radioactivity in the stomach from 120 seconds to 60 minutes later. These same authors (Am. Jr. Digest Dis. 8: 171-173, 1941) demonstrated a radioactive gastric secretion even from achlorhydric dogs following I. V. injection of $LiCl^{38}$.

Thus in gastric carcinoma there is the possibility of concentration of chlorine within the tumor. There is also a chlorine isotope, Cl^{38} with a 39 minute half life, strong beta and gamma emissions and decay to a non-toxic element. In normal stomach tissue, the difference in concentration of Cl between blood and gastric mucosa following histamine is about 1 to 20. Since gastric tissue is highly susceptible to radiation, it is possible that the dilution of body fluids and the concentration in gastric mucosa has a sufficient dosage differential to allow a cancerocidal dose to be administered. Wang (Jr. Gen. Physiol. 31: 259-268, 1948) recently demonstrated that the concentration of I. V. injected Cl^{38} in aqueous humor and in the cisterna magna very slowly increases to equilibrium with blood; for example, the Cl^{38} reaches about 50% of equilibrium level in aqueous humor in about one half life of the Cl^{38} . The only other concentration point for chlorine is in

the kidneys and, fortunately, kidney tissue is relatively radio-resistant.

Such a procedure would probably reduce the stomach to a non-functional fibrous sac which is easily taken care of surgically. It most likely would not concentrate the radioactivity in the metastatic tissues. Since these metastases are the main reason for surgical failure, an additional procedure would be necessary to concentrate dosage over metastatic areas. The main areas where surgical removal of metastases is impossible are in the hepatic pedicle, in diffuse infiltrations around surrounding tissues, and on implants firmly bound to vital structures. Since most of these metastases are in thin sheet-like structures a strong alpha emitter might be used as a surface paint direct to metastases. The disintegration series of Ac^{225} , Ra^{224} , Rn^{222} are all relatively rapid (4-10 days) and sufficiently energetic to penetrate sheet-like tissues. In small metastatic masses Hahn's infiltration technique with gold or shorter-lived isotopes could be used.

The tendency for heavy particles to produce fibrosis would be an asset in the hepatic pedicle because the fibrosis would occur slowly and encourage the development of a collateral circulation to the liver. This in turn would allow a free dissection of the pedicle, once the vulnerability of the hepatic artery was removed. It has been estimated by some surgeons that if all visible metastases could be thus destroyed about half of the early diagnosed cases could be saved. Questions of radiation sickness and damage to other tissues, however, cannot be estimated.

It is obvious that this suggestion for the treatment of a gastric carcinoma does not imply the use of a "magic bullet" which can be aimed straight at cancer cells alone. There are reasons for believing that the concept of a "magic bullet" is unreasonable. In the classical study of Lewis (Arch. t. Exp. Zellf. 23: 8, 1939) on strain 319 mouse sarcoma a careful review of the comparisons of malignant tissues with normal tissues showed no one item that completely distinguishes the abnormal cell. On the basis of judging single cells only statistical prediction of abnormality is possible. However, there are certain characteristics that are present to a greater extent in the abnormal tissues and might possibly open the way to producing a difference of dosage between normal and abnormal sites. Further, the idea that certain primitive cells or that cells in mitosis are especially susceptible has been doubted. Bloom (Radiology 49: 344-347, 1947) can find no evidence of such aids to the "magic bullet" idea.

However, the idea of a dosage differential rather than a magic bullet enlarges the field. To use the example of gastric carcinoma again, there is the possibility that the macrophage system could be used to concentrate the dose of radioactivity. It is known that there is a tendency for a macrophage organization in and around the malignant cells. Recent work by Pomerat (in Press) suggests the production of a macrophage producing factor which could increase macrophage activity in the area of malignancy. There is also some evidence that certain types of macrophages can be encouraged to wander along the same pathway as malignant cells. (I believe this is one of the ideas now being followed up by Brues at the University of Chicago). While it is unreasonable to expect a selective pickup of radioactive materials by only those macrophages within the tumor area, it might be possible to produce a sufficient difference in dosage between tumor and normal areas to allow the use of a substance generally selective by the macrophage system.

The dosage differential might be increased by use of a further combination of methods of applying the radioactivity to the malignant tissue. In the example of gastric carcinoma there could be an additional intra-viscus administration of insoluble radioactive materials by stomach tube. Brunschwag and Schnitz (Am. Jr. Digest. Diseases 8: 171-173, 1941) showed that insoluble AgCl^{38} will probably not pass the gastric barrier readily.

Figge and Company (Proc. Soc. Exp. Biol. and Med. 68: 640-641, 1948) find an interesting accumulation of injected porphyrins and metalloporphyrins in neoplastic tissues. A dosage

differential of radioactive zinc porphyrin might be sufficient in lymphatic metastases to work as a combination with Cl^{38} .

None of this can be started on patients without careful animal trial. However, the detailed animal experiments are obvious and relatively straightforward in design. A number of gastric pouch dogs are necessary, with careful determination of differential tissue selectivity of Cl^{38} in high dosage. The question of hepatic pedicle collateral circulation must be determined on large animals. The penetration depth possible with surface application must be determined and there must be a re-evaluation of the metastatic spread of gastric Ca from the standpoint of topical application or infiltration techniques. The question of dosage is most difficult and will probably depend ultimately upon human experiment.

We need not have used gastric carcinoma as an example. There are selective concentrations of various materials in other organs. The kidney is another good example, especially since normal kidney tissue is relatively radio resistant, and some of its tumors are highly sensitive.

Thus, a careful search for a specific idea which might possibly be used in the Oak Ridge program does not seem as difficult as it once did - as soon as the magic bullet and the leukemia concepts are dropped. By thinking in terms of relative tissue selectivity and by getting away from the very difficult leukemias into more simple (and numerically more important) neoplasms specific procedures open up readily. Such studies will not further an understanding of cancer; they would be empirical in the worst sense of the word, but the recent revelations of basic studies are pointing to no quickly reached corner around which is a cure. It might be that an empirical approach will get there first, in which case such studies are justified, and anyway, this is the type of study for which the money seems to have been appropriated.

One further approach to the problem might be available to the Oak Ridge program. This involves the use of accelerators. You already have my opinion on the usefulness of such machines in studying the effects of radiation in my letter of August 26. Since that report I have heard from many persons concerning the use of such machines. The radiologists are uniformly in favor of such studies especially if they can be in on the use of the machines.

Dr. Cowie of Carnegie Institution of Washington is highly impressed with the possibilities of the use of the large machines. He writes that "the use of a betatron as a source of stimulation of medical research groups as well as the laity in sponsoring research efforts is in itself sufficient justification, I believe, for the procurement of this instrument for the south and southwestern medical schools. This would provide suitable means to carry on research activities commensurate with other parts of the country where large super-voltage installations are now widely available.

"The procurement of such an instrument would also act as a magnet in attracting and keeping research men who desire to leave the south because of poor facilities of this sort."

Dr. Cowie offers the use of the Carnegie facilities for short lived isotope work in their cyclotron laboratories, and thus favors new betatron development rather than more cyclotron development.

Dr. John Lawrence (Univ. of California) writes that he has had a great deal of discussion

with various members of his staff concerning the question but cannot cite a unanimous opinion. However, he believes that a cyclotron should be available for the production of carrier-free short lived isotopes unavailable from the pile. "If the chief aim of the investigation is to be experimental cancer therapy or the study of local radiation effect, I would suggest the purchase of a betatron or of a very large cyclotron. 20 MEV betatrons have a good chance to produce somewhat localized irradiation." Both Lawrence and Cowie point out the necessity for a crew of highly trained specialists to run the machine.

Dr. Evans (M.I.T.) and Dr. Failla (Columbia) agree with the statements of Lawrence and Cowie, but Dr. Failla and Dr. Newell (Stanford) add suggestions on other accelerators which might be more versatile for a small program.

Thus, there is a great deal of enthusiasm for medical research with the large accelerators, and I believe they are an essential part of the Oak Ridge program. However, as I stated in previous letters, an accelerator program must be considered secondary to our primary purpose of working with materials already available at Oak Ridge.

If the opportunity for getting one of these machines arises, I believe we should jump fast. However, I don't believe the Board should initiate a recommendation for acquiring an accelerator at Oak Ridge until the Medical Program is well under way. I propose that the whole question be laid aside until next spring.

s/ Marshall Bruwer
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