(cf. item 63) IB-236

File Reference: General Information on Therapeutic Applications - 728138

Excerpt from letter Dr. B.V.A. Low-Beer to Dr. J.G. Hamilton, April 2, 1946.

In accordance with your request of statistical figures for leukemia, lymphosarcoma and polycythemia vera in this department, I wish to inform you as follows:

In the period from January 1943 to December 1945 73 patients were treated for chronic, myelogenous and lymphatic leukemia. In the period from January 1943 to December 1945 23 patients were treated for polycythemia vera. In the period from January 1943 to December 1945 49 patients were treated for different types of malignant lymphomas.

From these data the polycythemia vera cases appear most significant because in these cases radioactive phosphorus exclusively was used as method of treatment, in 1943 1 patient, in 1944 8 patients, and in 1945, 13. At the present time, that is, April 1946, I have 5 patients lined up for treatment. None of the leukemia or lymphosarcoma cases were treated exclusively with radioactive phosphorus. On the contrary, I would say that most of the patients have been treated with x-ray therapy because of insufficiency of the amount of radioactive phosphorus supply.

In addition to the above mentioned disease groups we are using radioactive phosphorus for topical application in skin lesions, namely basal cell carcinoma, hyperkeratosis, warts and hemangioma. In the period from 1943 to 1945 we have treated approximately 350 lesions.

As to my opinion about the efficiency of radioactive phosphorus in different types of lesions, I should like to state that in leukemia the treatment with radioactive phosphorus is a very convenient type of treatment and is a very good means to keep in control the blood disorder. However, radioactive phosphorus does not prevent the ultimate fatality of the disease. Neither does any other type of treatment. It is rather difficult to make a comparison between radioactive phosphorus and total body x-ray treatment. It has been my experience that in some instances where control with one type of treatment could not be achieved, the other type of treatment brought about the intended remission of the disease process. However, it can be stated that radioactive phosphorus in the treatment of leukemia plays as important a part as does total body x-ray treatment. It is accepted by our hematologists that these two types of radiation are superior to any other type of treatment for leukemia.

As to malignant lymphomas, again a combination of both types of radiation treatment is preferable to local treatment with x-rays only.

In polycythemia vera treatment with radioactive phosphorus is superior to any other type of treatment. I have patients with complete remission since January 1943. Although we know that radioactive phosphorus is not a "cure" for polycythemia vera, we do know that a complete remission has been almost invariably achieved with 2 courses of treatment, 4 weeks apart, and lasting for 4 years or longer, and also this method of treatment approaches the strictest criteria concerning control of an incurable disease.

Finally, the treatment of skin lesions with topical application of radioactive phosphorus has proven 90% of the cases, including the skin malignancies, a curative mehtod of treatment.

From our statistical data it is evident that the number of referred patients for radioactive phosphorus treatment is on a rather rapid increase; therefore I believe that for the next 6 months the request for 1.2 to 1.5 curies per month will just cover the requirements. *******

8002588

Excerpt from letter J. G. Hamilton to P. C. Aebersold April 4, 1946 -

I have spent some little time discussing with both Doctor B. V. Low-Beer and Doctor John H. Lawrence the situation in respect to P 32 and its use in the San Francisco Bay Area. I think that a brief discourse of the experiences whithin this local area, in a sense, may serve as a small scale model for the ultimate situation in regard to the nation as a whole. I am enclosing a letter from Doctor Low-Beer which gives in considerable detail, their experiences with radioactive phosphorus. However, I think it is of value to summarize in this communication both the experiences of the University of California Medical School as well as those of the Radiation Laboratory.

At the University of California Medical School, under the direction of Doctors B. V. Low-Beer and Robert S. Stone, a total of approximately 150 patients suffering from various types of blood dyscrasias were treated with radioactive phosphorus. This embraces an interval extending through the years 1943, 1944, and 1945. In addition, they have developed a very interesting and successful technique of treating superficial malignant skin lesions by a surface application of radioactive phosphorus and during the same three year interval, a total of 350 lesions were treated with P 32. It may be of interest to break down the patients treated for various types of chronic blood disorders: of the total of approximately 150 individuals, 73 were suffering from various types of leukemia, 49 had different types of malignant lymphomas, and there were 23 cases of polycythemia vera.

Doctor Low-Beer appraises the value of P 32 in the treatment of leukemia in the following manner. He feels that it is an excellent method for keeping the blood disorder under temporary control although it must be clearly understood that the radioactive phosphorus does not prevent the ultimate fatal outcome of this condition. A comparison of radiophosphorus with the most effective methods of x-ray treatment for the control of leukemia indicates that not infrequently adequate control of the disease can be secured temporarily where the results from x-ray have been satisfactory. In addition, he indicates that a combination of x-ray and radioactive phosphorus for certain of the lymphomas is significantly superior to treatment with x-ray alone.

Leukemia

Lymphoma

The situation with polycythemia vera is quite different. Here, the radiophosphorus is the only method of treatment thus far developed that will adequately induce complete although temporary recovery. This temporary recovery of remission has extended in their small group of patients through a period in excess of four years, and as he states, P 32 therapy approaches the strictest criteria of control of an incurable disease.

Polycythemia

The surface or topical application of P 32 for the treatment of skin malignancies has proven curative in approximately 39% of the cases. This of course, is not a comparable situation to the other conditions described above inasmuch as these skin lesions can be successfully cured in a high proportion of cases by x-ray and surgery. However, Doctor Low-Beer feels that there are many advantages in using P 32 over the older methods of treating these skin conditions.

Skin cancer

A brief summary of the work done here at Berkeley by Doctor John H. Lawrence and his associates reveals that a total of 570 patients have been treated with

P 32 since 1938. Of this group, there were 340 leukemias, 80 patients with lympho-sarcomas, and 150 patients with polycythemia vera. It is also of interest to note the increase in new patients treated per year; starting in 1938, there were 10 patients, 20 in 1939, 40 in 1940, 90 in 1941, 100 in 1942, 150 in 1943, 200 in 1944 and 250 in 1945.

Doctor Lawrence's appraisal of the significance of P 32 in the treatment of leukemia, lymphomas, and polycythemia vera parallels very closely the views held by Doctor Low-Beer. Doctor Lawrence feels that P 32 is superior to x-ray for the control of leukemia and lymphomas. From his records, it is certain that life expectancy with P 32 as the therapeutic agent is equal to and possibly greater than with x-rays. In the case of polycythemia vera, there is no question that the life expectancy with radiophosphorus treatment is much greater than the results that have been reported by other investigators using x-rays, drug therapy, bleeding, etcetera, in an attempt to control this condition.

In brief, it seems to be the opinion both in Berkeley and at San Francisco that P 32 is significantly superior to the treatment of leukemia, and lymphomas to other standard methods of therapy and in the case of polycythemia vera, P 32 is truly a life-saving agent.

The demands for both San Francisco and Berkeley during the next six months for P 32 are as follows: 1.2 curies per month for the Medical School and 600 microcuries per month for Doctor Lawrence's group. While the latter group has had significantly larger numbers of patients under treatment per year, I feel that the more abundant request for the San Francisco group is by virtue of the fact that they now only are treating a relatively small proportion of the patients with radioactive phosphorus due to the limited supply. Moreover, in San Francisco, a significant fraction of the P 32 is being used for the treatment of skin lesions and for study of tumor metabolism using clinic material.

With an adequate supply of P 32, the annual number of patients treated between Berkeley and San Francisco would probably total about 500, exclusive of therapy of skin cancer and tracer experiments. The average patient, during the year interval, will require from 10 to 25 millicuries of radio-phosphorus, assuming a rather generous annual average level of 20 millicuries per patient. This leads to a value of 10 curies per year or slightly less than 1 curie per month. However, the material has been made available roughly once a month. Therefore, this figure should be multiplied by at least a figure of 2 to allow for decay of a portion of the P 32 during the month, since it is neither practical nor desirable to treat all of the patients during the first few days of each month.

On this basis of an estimate of the past and future consumption as Berkeley, I believe that a reasonable prediction of the amount of P 32 required for the nation as a whole can be made insofar as the treatment of leukemia and allied conditions is concerned. The estimated annual incidence of chronic myelogenous and lymphatic leukemia, together with the malignant lymphomas which do respond moderately well to P 32, notably lympho-sarcoma, amounts to roughly 5,000. While the total amount of radiophosphorus required to treat each new patient will range from 15 to 40 millicuries, it is observed that at least twice this amount of P 32 must be produced due to the factors of decay arising from the causes related above. With this consideration in mind, it would appear to me

that 50 millicuries would be a reasonable amount to allocate to each new patient at the time the material is sent to the clinics using it. In addition, 500 to 1000 new case per year of polycythemia vera may be anticipated and here again the average amount required for each patient during his life span will be of the order of 25 millicuries.

Therefore, a total of 300 curies per year would represent a reasonable estimate of the national requirement of P 32 once this material could be distributed to appropriate and suitably qualified medical centers for their effective use.

I would suggest as a possible method of starting a nation-wide program in distribution of radioactive phosphorus, that during the first six months, say from July 1946 to January 1, 1947, that five to ten large medical centers who have had experience in the use of P 32 be supplied with adequate amounts for full scale therapeutic use. Such centers might include Washington University at St. Louis, Billings Hospital in Chicago, Mayo Clinic, Rochester, Minnesota, the University of Ohio Medical School, the University of Michigan at Ann Arbor, the University of Rochester Medical School, Harvard Medical School , Memorial Hospital in New York, the University of Pennsylvania Medical School, Jefferson Medical College, and the University of California at Berkeley and San Francisco. In addition to this list, Western Reserve and the Swedish Hospital at Seattle might also be included, in that at the former institution, it is my understanding that Colonel Friedell is shortly to join the faculty there in the Division of Radiology and that Doctor Simeon Cantril is in charge of the Tumor Clinic at the Swedish Hospital.

While it is difficult for me to appraise the number of leukemia patients these institutions might anticipate during such a six months interval, I am sure that amounts ranging from 100 to 500 millicuries and possibly more could be effectively utilized per month. Certainly a total of from 30 to 50 curies of P 32 could be used during the 6 months interval ending January 1, 1947. A prediction of the rate of increase of consumption of P 32 during 1947 is difficult to make with any degree of accuracy. The best I can estimate is a guess that it will fall between 100 to 200 curies during the twelve months period.

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File Reference: General Information on Therapeutic Applications.

IB-4 38

Excerpt from Dr. E. E. Zirkle to P. C. Aebersold, April 9, 1946 -

This is a partial answer to your letter of March 28 concerning national demand for P 32 for therapy. Because of absences from the campus, I have not yet secured all of the extractable information from the local group. However, Dr. Jacobson estimates that the University of Chicago Clinics would use, if available, 1 curie during the year 1946-46, and 2½ curies during the year 1946-47. These estimates makes no allowance for losses due to radioactive decay during storage. *****

Excerpt from letter Dr. Sherwood Moore to P. C. Aebersold, April 12, 1946 -

It is my considered judgement, having received numerous "wild" requests for P 32 following a publication in a popular magazine, that the use of P 32 and any other isotopes should be restricted to medical schools or class A hospitals. This does not mean that the patients need be hospitalized. Isotopes should be supplied from some central source, whether by government or commercial concerns makes no difference. Certainly the development of isotope treatment and research has gone far enough that educational institutions should not be burdened with the expense of their production.

As to the amount of P 32 for justifiable therapeutic use for the nation, this question cannot be answered because there are no reliable data on the number of cases suitable for this form of therapy available in the United States. I speak advisedly on this statistical question because, as a member of the National Advisory Cancer Council, I can tell you there are no reliable figures for the number of cases of cancer in the United States, this without reference to one of the subdivisions of malignant disease such as leukemia is.

Excerpt from Letter Dr. F. A. Hodges to P. C. Aebersold April 9, 1946.

As to the estimates which you quoted concerning the probable total amount of P 32 which might be demanded for the treatment of leukemic patients, I can only say that the word "guess" was advisedly chosen. Perhaps if with the aid of F.B.I. agents every patient known to be suffering from some form of leukemia could be apprehended and dragged into a hospital, the amount of P 32 mentioned in your letter might actually be administered to humans for therapeutic purposes in one twelve months period. The amount seems utterly fantastic to me, however, particularly in view of what I understand to be present thought regarding the efficacy of radioactive phosphorus. Unless I am greatly mistaken all of the observations to date boil down to the belief that P 32 can accomplish everything that external radiation does and perhaps a little more adroitly.

It seems to us that the wide variety of ideas which various investigators who never before have used isotopes, either stable or unstable, are presenting for discussion indicates that it would be much more profitable to make a wide variety of isotopes available rather than astronomical quantities of phosphorus only.

I nearly neglected to mention in answer to your specific question other localities where I believe interest will be found. You have not mentioned Dr. Doan of Ohio State University at Columbus. He has been active with P 32 in the past. You did not mention the University of Rochester although I am certain that Dr. Dowdy is cooperating with you.

Both Lampe and I have grave concerns regarding the unlimited and uncontrolled distribution of radioactive materials. Certainly it would seem wise to us to limit the distribution very stringently to a few closely controlled institutions, at least until definite plans based on experience and careful thinking can be developed.

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File Reference: General Information on Therapeutic Applications

I-3

Excerpt from letter Dr. R.D. Evans to Prof. Lee DuBridge, April 10, 1946.

You must have some mechanism for judging the competence of thos who request radioactive material. This problem has turned out to be less difficult than we originally imagined it would be. The great bulk of applicants divide quite sharply between those who are competent and those who are not. There are very few intermediate cases. Re-examination of the cases which we have regretted show that they were usually due to bad judgment on our part or to political pressure.

In the case of foreign shipments we deliver the radioactive material to a consul or embassy, and require that they take full responsibility for foreign delivery and proper use.

The information required on the request card gives a pretty good first order estimate of competence, because the worker must know something about radioactive units, must be able to compute radioactive decay, and must be able to explain their project clearly. The professional standing of new applicants can usually be judged from their description of their project, from their previous research publications, from their sponsorship by foundations or groups administering grants-in-aid, or by the physicists whom they may cite as collaborators. The amounts of radioactive material needed are usually small, but the applicant should be made aware both of health safeguards and of the hazards of general radioactive contamination of his own laboratories through careless handling or spilling of the material.

The Federal Food, Drug, and Cosmetic Act, in Section 505(h), Regulation 2.111, restricts the use of new drugs to those who have adequate facilities for investigation, and who will make full reports of their findings to the Food and Drug Administration. The medical director of the Food and Drug Administration has ruled that Section 201 of the Act places all artificially radioactive substances used for medical research or for therapy under the classification of "new drug." This automatically places a Federal restriction on your distribution plans, and requires that the materials be supplied only to competent investigators. In the case of each radioactive substance the Food and Drug Administration is willing to make recommendations concerning specific types of biological experiments, on a basis of which they will consider reclassification of the isotope from "new drug" to "drug." Experiments of this sort are now under way for 12-hour iodine and 8-day iodine.

I feel rather strongly that any recipient of materials from Clinton Laboratories should be required to have radioactivity measuring equipment available, either counters or electroscopes. This is essential because even the therapeutic applications require dose and tracer monitoring.

The question of beta ray standards is being worked on intensively by the Committee on Standards of Radioactivity of the National Research Council and in the reasonably near future standard sources will be available through the National Bureau of Standards, who will also test and evaluate commercially manufactured counting equipment and electroscopes.

In all cases I believe that a charge should be made for radioactive materials supplied. Even surplus Government property is sold, not given away. The necessity of paying for the radioactive material will act as an important filter to screen out casual requests. Even the production costs of therapeutic quantities of

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phosphorus and iodine isotopes by cyclotron bombardment is often cheaper than equivalent X-ray or surgical treatment. Pile production should reduce these costs even further. The Committee on Growth is allocating funds for the pruchase of isotopes, and it is in accord with the policies of those who administer grants-in-aid to provide for payment for chemical supplies. The National Institute of Health and I believe the Navy Office of Research and Inventions are also willing to allocate funds to their contractors for the purchase of radioactive supplies.

We have found it highly desirable to have a fixed minimum charge, in our case $20 for any shipment of radioactive material however small.

There are a number of actual and potential industrial uses of radioactive isotopes which are very important. Provision should be made for distributing isotopes to competent industrial concerns who may wish to use them in plant process development, quality control of products, trade marking, as well as in basic research. Industrial concerns who have well-developed plans for the large scale use of radioactive isotopes on problems which cannot be solved in any other way include Du Pont, Republic Steel, Owen Corning, American Viscose, Bausch and Lomb, and N. E. Coke.

The future application of radioactive isotopes in the field of industrial hygiene is extremely important. Goodman and Irvine did some pioneer work here several years ago on mercury poisoning using radioactive mercury, and a very nice over-all picture of the future use of isotopes in industrial hygiene has been given by Cantril in INDUSTRIAL MEDICINE 15:1, 37 (1946). * * * *

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File Reference:
General Information on Therapeutic
Application .

IB-4

Excerpt from letter R. D. Evans to P. C. Aebersold, April 13, 1946 -

This is in response to the request in the fourth paragraph of the letter of 3 April 1946 for a statement on the therapeutic use of radioactive isotopes. It is clear from the literature (Journal of Laboratory and Clinical Medicine 31:107 (February 1946) by Dr. Carl V. Moore et al) that P 32 is the treatment of choice in policythemia vera, and that it is a useful therapy for some types of leukemia but not for others. Two papers, one by Hertz and Roberts and one by Chapman and Evans will appear in the Journal of the American Medical Association shortly after 1 June 1946 on the therapeutic use of I 130 (12.6 hour) in the treatment of Graves' disease. The 8-day isotope I 131 will undoubtedly be useful therapeutically, but much clinical research remains to be done before the dosages and possible late after effects of this isotope are worked out.

As you will see from paragraph 8 of my letter of 10 April 1946 to Professor Du Bridge, none of the artificially radioactive isotopes have yet been classified as "drugs" b y the Federal Food and Drug Administration. This means that these isotopes are only available for experimental use, and by competent research clinics who on request will report all findings to the Food and Drug Administration. Each radioactive isotope must be evaluated for its possible long-term harmful effects before being reclassified by the Food and Drug Administration from "new drug" to "drug." Until this type of experimental work has been completed to the satisfaction of the Food and Drug Administration no radioactive isotopes should be distributed for what might be called "routine therapy". Every shipment of radioactive isotopes should be labelled "Caution--New drug-Limited by Federal Law to Investigational Use" and the material should be supplied only to established competent investigators.

I feel very strongly that everyone using radioactive isotopes therapeutically should have available radioactivity detection equipment with which to make tracer studies on their patients, excretion studies, and to verify all administered dosages.

An estimate of the national requirements for the experimental therapeutic use of isotopes is difficult to make. Based on our experience in this field I would guess that something of the order of 500 millicuries of P 32 per week would take care of current legitimate requirements. For example of a large and very active group like the Mayo Clinic uses only about 60 millicuries per week. The legitimate requirements for 8-day iodine are harder to estimate, but I should think that the initial requirements by competent clinical research groups might be of the order of 100 to 300 millicuries per week.

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NOTE: (In letter from Prof. J. M. Cork) Dr. Bethel, Ann Arbor, can use 30 mc/week throughout the year or approximately 1.5 curies/yr.

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Excerpt from letter R. S. Stone to P. C. Aebersold, May 23, 1946.

Information has reached me that you were rather anxious to know whether low specific activity radiophosphorus would be acceptable for therapy or tracer work. My own reaction is rather violently against even the idea of low specific activity material. In fact, I think that in many instances the highest possible specific activity, namely the activated element without carrier, would be absolutely best for therapy or tracer studies. There are, of course, certain practical considerations that would make the use of the carrier-free material rather difficult, but the closest approach to this ideal should be attained.

I asked Doctor B.V. Low-Beer and Mr. Scott to write me concerning their opinions and I am enclosing their letters.

I know that you and whatever committees have this matter under consideration will give it the attention it needs.

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Excerpt from letter Dr. K. G. Scott to Dr. R. S. Stone, May 15, 1946.

In my opinion, radiophosphorus without carrier is much more usable in biological experiments upon small animals. It is difficult and often impossible to gain information regarding phosphorus in their biological systems if large amounts of inactive phosphorus are given along with the P 32, since this inactive phosphorus saturates the body and masks the effect which carrier-free P 32 might demonstrate.

In addition, some retention studies we did in mice showed that the retention of phosphorus of high specific activities by mouse tumors was considerably higher that P 32 which contained large amounts of inactive phosphorus. When an isotonic solution of sodium phosphate from a probe sample prepared in the cyclotron was given (1000 microcuries per cubic centimeter), uptakes by tumor greater by a factor of two were observed than when phosphorus containing but 100 microcuries per cubic centimeter of isotonic phosphate solution was administered to mice. This would suggest that phosphorus without added carrier would be a far more useful agent therapeutically than that with carrier. The one sample of P 32 plus sodium acid phosphate received by this laboratory contained but 55 microcuries per cubic centimeter of isotonic solution at the time it was received. The presence of such large amounts of inactive phosphorus make such solutions dubiously useful for animal experimentation, difficulty useful for human administration.

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Excerpt from letter Dr. Low-Beer to Dr. R. S. Stone, May 16, 1946.

With reference to our conversation concerning the advisability of using low or high specific activity radioactive phosphorus, I wish to make the following statement: Phosphorus, as an essential mineral metabolite, is provided by daily food intake. With a normal mixed diet this requirement is amply covered. As a matter of fact, only part of the phosphorus from the daily food is absorbed by the intestine, while the other part passes through the gastro-intestinal tract without being absorbed by the intestines. Phosphorus is so widely distributed in the animal and plant world that it is impossible to provide a phosphorus free calorie-adequate diet. The ubiquity of phosphorus compounds brings up the question whether an inorganic phosphate salt is absorbed by the intestinal tract

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to the same extent as organic phosphate compounds or the inorganic orthophosphoric or pyrophosphoric derivatives. The question is not solved whether or not it is necessary that the phosphorus requirement of the body be at least partially provided by organic phosphorus compounds.

The daily average requirement of phosphorus of an adult human being is approximately 0.88 gms. The utilization of phosphorus in the intestinal tract depends not only on the presence of phosphorus in the diet, but much more on other factors. The acidity or alkalinity of the stomach influences greatly the utilization of phosphorus by the intestines. Acidity promotes utilization. The presence of certain cations in foodstuff also influences the utilization of phosphorus. The presence of iron, calcium, magnesium, aluminum, beryllium, manganese, (the latter three even in tracer amounts) hamper the utilization of phosphorus because of the formation of insoluble phosphates. High fat content of the diet is also disadvantageous to utilization. For these reasons the food content in phosphorus must be higher than the daily requirement. Approximately 1.3 gm. of phosphorus are necessary in the daily food intake in a mixed diet to provide the necessary 0.8 gm. daily body requirements, assuming ideal conditions of the ratio between promoting and counteracting substances in the food. An attempt to increase phosphorus utilization by increasing the amounts of phosphates provided in diet is not possible so far as our present knowledge goes. For instance, by giving inorganic phosphate compounds in the pre or post-absorptional stage of ingestion, the utilization is not additive. The intestines react by an irritative state which manifests itself in diarrhea. The phosphorus compound passes the intestinal tract rapidly without utilization. Other regulative mechanisms such as changes in pH, changes in excretion of calcium in the large bowel, etc. result.

For phosphorus absorption through the intestinal wall and entrace into the blood stream, other regulating mechanisms come into play. Administration of the total daily requirement in a single dose in the preabsorptive stage (this means fasting state) will lead to phosphorus depletion. The reason for this is the following: The normal phosphorus level of the blood varies between 2 to 4 mg.%. Any increase or attempted increase is immediately regulated by increased excretion, mainly by urine and partially by stool. Thus when phosphorus is absorbed rapidly through the intestine, it will shortly afterwards appear in urine to a great extent. This is the reason that all attempts to increase phosphorus utilization by giving excess amounts of phosphorus orally or intravenously have been unsuccessful.

With respect to radioactive phosphorus, I object to the use of weak specific activity samples in therapy as well as in tracer work for the following reasons:

In tracer work: The body, being unable to differentiate between active and inactive phosphorus, will indiscriminately take and utilize the phosphorus offered. Consequently, with a weak specific phosphorus sample, the concentration of radiation per cell or per unit tissue will be such that it will simulate low differential uptake.

Therapeutically an inadequate radiation concentration or radiation level will result. The suggestion to give leukemia patients more frequent doses involving larger amounts of total phosphate, and to wait until hematological changes occur, will result in a long wait and little effect. If I compare it with external radiation, that is, with x-rays, it would be as though one were to give daily say 1 r, or twice a day 1 r or three times a day 1 r, and wait and see what happens to the blood count. It has been experimentally shown that nothing happens to the blood count, at least nothing therapeutically satisfactory. However, it must be

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realized that such treatment involves considerable man power and man hours, for giving the treatment and for doing repeated blood counts. Further, such treatment would be a departure from our intention to plan and execute radiation therapy scientifically. Since the utilization of phosphorus is such a complex mechanism, the suggested use of weak activity by just giving more phosphate solution and more often such a solution, and waiting and watching appears to me as though one would suggest expressing dosage in milliampere seconds. There might be objection to my statement that we can achieve satisfactory radiation concentration in the body with radioactive phosphorus, and it could be said that by repeated doses we finally get the proper concentration. This conclusion is erroneous for the following reasons: in order to achieve a beneficial hematological effect in leukemia with radioactive phosphorus, the cell destruction must be faster than cell regeneration. In order to achieve this, a certain radiation concentration or radiation level must be in the body. Naturally an excess leads to a destruction not only of the white cells but also the red cells. A low radiation level, on the other hand, will be inadequate to bring about the satisfactory and differential destruction of leukemic tissue. This fact is well established experimentally and has been observed clinically.

Although it is not possible to state exactly what radiation concentration or radiation level is the desirable one in an individual case, we know empiracally that approximately a 3 to 4 millicurie level with a 400 to 500 microcurie/cc phosphorus brings about satisfactory radiation response. Assuming an activity of 1 microcurie per 1 mg. of phosphorus (not phosphate), then for 800 microcuries a total of $2\frac{1}{2}$ gm. phosphate must be administered. If this were administered orally and if it were absorbed entirely from the intestine, (which the intestine is incapable to do as explained before), the blood phosphorus level would increase by approximately 700% on the basis of the following calculation:

Assuming that the total blood volume is 5000 cc., then the plasma volume is approximately 3000 cc. Since the normal phosphorus blood level is approximately 4 mg.%, 800 mg. will result in an increase of 700%. Even if the absorption doesn't take place instantaneously but over a period of say, 1 hour in a fasting patient, then there will still be a considerable increase above the physiological level which will result in excretion. The situation will be worse if we should try to administer this low activity phosphorus intravenously. As to the use of radioactive phosphorus in polycythemia vera, where we deliberately treat with larger doses, the desirablilty of high specific activities is even more evident. I have done urine excretion studies in 3 patients which showed the following: When using 200 microcuries/cc phosphate solution and a total amount of 6000 microcuries were given in one single dose, which is equivalent to 450 mg. phosphate or approximately 150 mg. of phosphorus, then an average 750 microcuries were excreted in the first 8 hours; 500 microcuries in the second 8 hours, and 300 micorcuries in the third 8 hour period after intravenous administration of the material. In the second patient, the total excretion in 24 hours was as high as 2300 microcuries. In the third patient, approximately 500 microcuries/cc were used and the dose was divided into three 2000 microcurie doses given on succeeding days. I found that the excretion in 4 days was 680 microcuries. If we calculate this to a total phosphorus content, the explanation for this difference in excretion becomes absolutely evident.

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6000 μcs 200 μc/cc 15 mg/cc
is equal to 30 cc. solution = 450 mg. phosphate or
approximately 150 mg. phosphorus = 5 mg. per cent increase.

2000 μc daily 500 μc/cc 15 mg/cc
is equal to 4 cc. solution = 60 mg. salts aproximately
20 mg. phosphorus = 0.6 mg. per cent increase.

On the two subsequent days, even with slightly larger amounts of solution, the total phosphorus daily administered is not more than 23 mg. in one dose.

In conclusion I would like to turn your attention to the fact that in the five years I have been working with radioactive phosphorus, I have always asked for higher specific activities and I have objected to low specific activities for the reasons I pointed out above. I would advocate that for treatment of polycythemia vera activities between 1500-2000 micorocuries/cc/15 mg. salt would be preferential. I would suggest similar activities for treatment of leukemia patients.

I am aware of the fact that I have not taken into account all factors which play a part in the utilization of phosphorus but I feel that my statement would have become too eleaborate.

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