Selective Inductive Heating of Lymph Nodes *

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OUR WORK on the clearing of surgically removed specimens of carcinoma of the colon and rectum and especially the clearing of the retroperitoneal tissues of patients who died in the immediate postoperative period [1, 2] convinced us that a new method was needed to destroy metastases in lymph nodes missed at operation. The outstanding facts of these studies made on patients in whom the surgeon thought that he had removed all demonstrable cancer were: 1) the pathologist was unable to demonstrate any metastases in retroperitoneal lymph nodes when an ordinary postmortem examination was performed, although all three of the patients examined in this manner had node metastases in the operative specimen; 2) in eight postmortem examinations all of the retroperitoneal tissues were cleared and 160 to 180 lymph nodes were charted and sectioned in each specimen. Of the four who had no demonstrable metastases in the retroperitoneal tissues, two had involved nodes in the surgical specimen and two had no lymphatic metastases in the surgical specimen (Fig. I). The four who had lymphatic metastases remaining in the retroperitoneal nodes also had involved nodes in the surgical specimen.

Drawings of these four postmortem preparations showed that all of the involved nodes were less than 1.5 cm. outside the operative field in three and even in the fourth the involved nodes would probably have been removed by present technics (Fig. II). The important point is that in these instances when such lesions could be found, the remaining *metastatic cancer involved only a small part of the node.*

Our studies [2] showed that cancer spreads through the lymph system by tumor embolism and the emboli are retained in the node in which they land. Lymph channels are not blocked by tumor, except in advanced cases; cancer does not break through the capsule of a node until very late when there is extensive lymphatic involvement; particles less than one micron in diameter will not pass through a lymph node even when the suspension containing them is injected directly into a lymph channel under 100 cm. of water pressure, and finally, injections into living patients showed that we could inject suspensions of carbon one micron or less (Fig. III) in diameter and fill the normal part of a node with the carbon even when the node was largely replaced by cancer.

Thus, our studies showed that in patients where the surgeon thought that he had removed all of the tumor, metastases in

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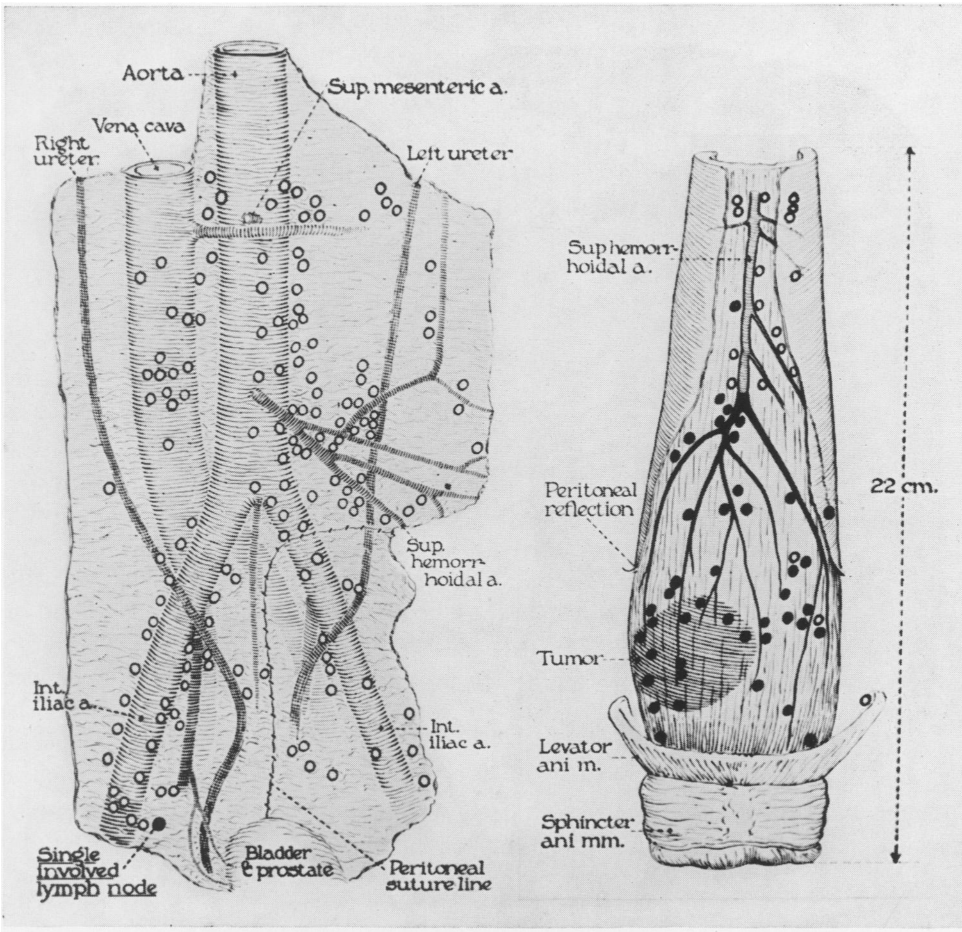

FIG. I. Operative specimen of carcinoma of the rectum known to be present one year, having 43 nodes (solid black dots) containing metastases. Postmortem showing one node containing cancer one centimeter outside the field of resection. Only a very small part of this node contained cancer.

lymph nodes not removed at operation involved only a small part of the node and particulate matter at least one micra in diameter could be injected so that it would fill the normal part of the node.

In 1941, a warning about heating of metallic foreign bodies when the patient was subjected to induction heating started us on this 16-year search of a method to pasteurize the nodes which contain cancer metastases missed at operation.

We planned to locate fine magnetic particles in the desired lymph nodes by injection before or at the time of operation. The usual resection would be performed removing most of the involved nodes and the injection site. The nodes surrounding the field of resection would contain the injected metallic particles. These could then be subjected to induction heating to destroy the metastases. This method would be applicable especially in carcinoma of the breast, stomach, lower rectum, bladder and prostate.

Previous workers[4] have reported that ordinary diathermy is contraindicated when

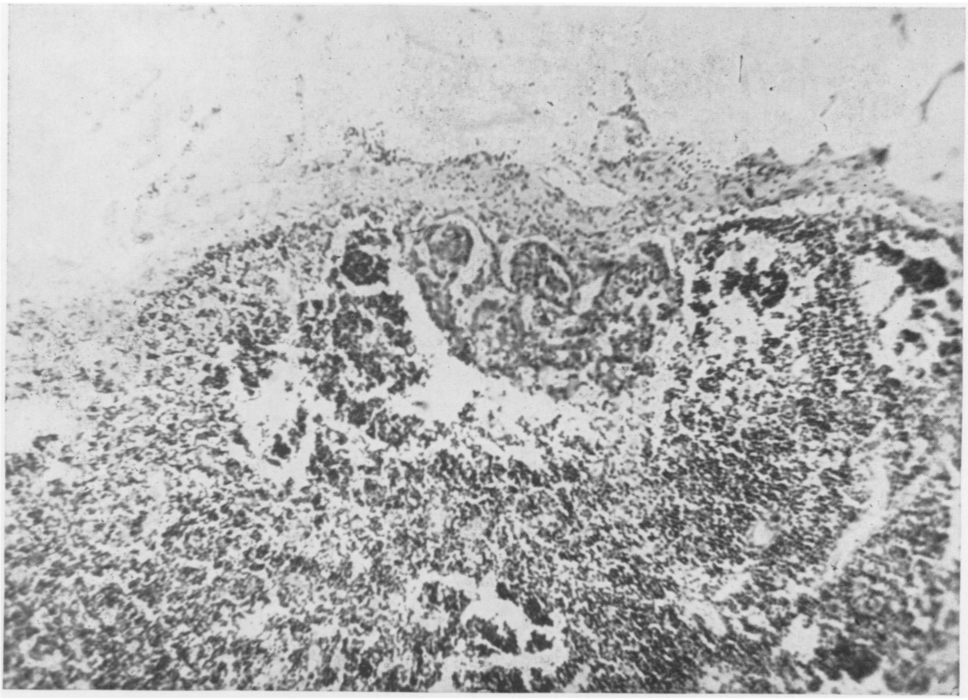

FIG. II. Total amount of cancer in single involved node remaining in postmortem preparation.

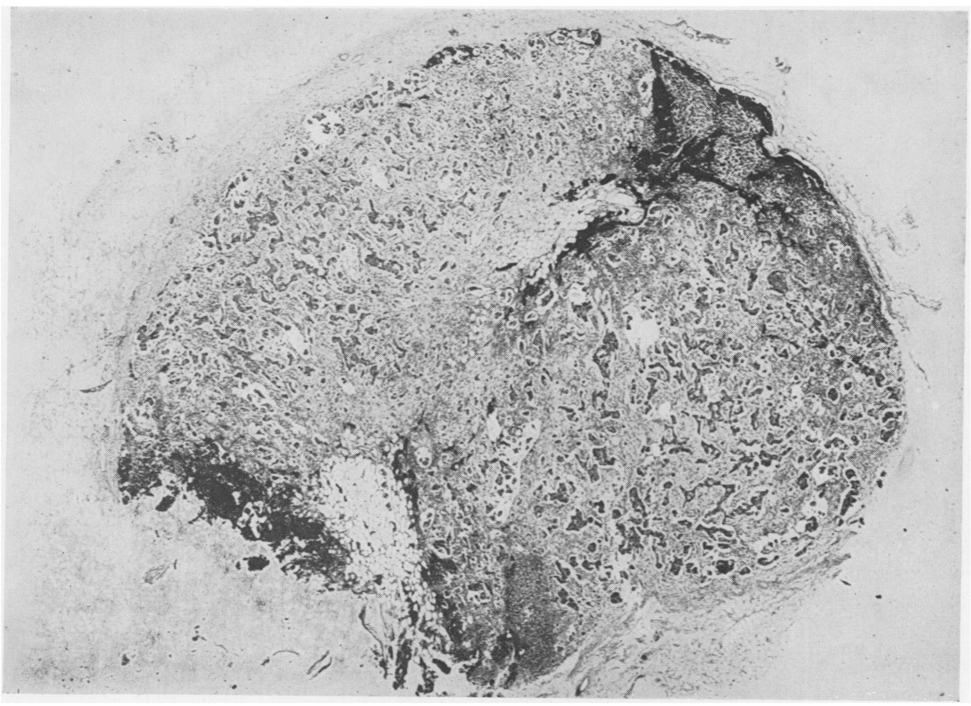

FIG. III. See page 599 for legend.

FIGURE IV. *Equation #1*

$$P_D\left(\frac{\text{watts}}{\text{in.}^3}\right) = 2\pi f G^2 K \tau \times .022 \times 10^{-12}$$

where

f = frequency in cycles
G = voltage gradient in dielectric $\left(\frac{\text{rms. v.}}{\text{inch}}\right)$
K = dielectric constant
τ = power factor of dielectric

FIGURE V. *Equation #2*

$$P_E = Ef^2 B_{max}^2 d^2$$

where

E = eddy current coefficient
f = frequency in cycles
B_{max} = max flux density
d = particle diameter

there is inflammation in lymph nodes, since it causes a hyperemia, then interference with venous return and then necrosis. We expect that such a process will be produced in nodes containing cancer. With the rise in temperature caused by heating the metal, necrosis of the node can be controlled by proper field strength and duration of heating.

Early experimental work was directed toward selection of a powdered material which would heat appreciably at radio frequencies and which was fine enough to be injected hypodermically into lymphatic channels.

Heating of a material in an R. F. field is caused by three effects: 1. Dielectric loss; 2. Eddy current; and 3. Hysteresis.

Generally, the tissue will be heated by dielectric loss and to a lesser extent by eddy current loss. Therefore, it is desirable to minimize dielectric heating. Any conductive material inserted into the tissue will be heated by eddy currents, and any magnetic material injected will be heated by hysteresis.

Dielectric heating occurs in any material which is not a good conductor when exposed to an electromagnetic field. The loss, and hence heating, per unit volume of dielectric is shown in Figure IV.

Since the power factor of the body tissue increases with frequency, the dielectric heating effect on body tissue will increase more than proportionally as the frequency is raised.

Eddy current loss occurs in conductive material in an electromagnetic field. The changing field sets up eddy currents in the material and causes heating due to the electrical resistance of the conductor. The eddy current heating per unit volume of material is shown in Figure V.

In testing non-magnetic metallic powders, it was found that as the particle size was reduced to a point where the material would pass through a No. 27 hypodermic needle, the heating of the non-magnetic particles was reduced to a negligible amount as shown in Figure VI.

Hysteresis loss, which is a form of magnetic friction, offered the best approach to the problem as the heat per unit volume is independent of particle size. This permits heating of suspended particles as small as .01 micron. As hysteresis loss is dependent upon the shape of the magnetization curve of the material, it is difficult to write an exact equation for the loss per unit volume; however, for the material and flux densities with which we have been working, it can be approximated by the formula shown in Figure VII.

FIG. III. Photomicrograph of lymph node almost completely replaced by carcinoma metastases. The normal parts are seen as dense, finely granular areas. A suspension of carbon particles was injected into the lymph channels in the neighborhood of the carcinoma of the breast. Most of the carbon is seen in the normal part of the node. Although some of it penetrates a short distance along spaces between the cancer cells, a part of the lymph sinus which is involved with carcinoma also contains carbon particles. Two areas of fatty degeneration are seen.

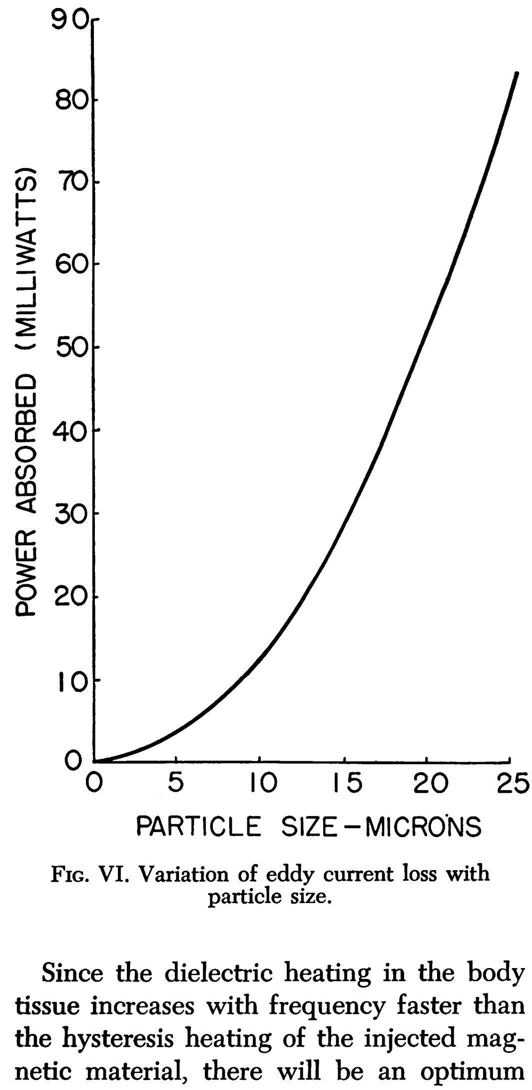

FIG. VI. Variation of eddy current loss with particle size.

Since the dielectric heating in the body tissue increases with frequency faster than the hysteresis heating of the injected magnetic material, there will be an optimum value of frequency which will permit greatest heating of the magnetic material without damage to normal body tissue. For the magnetic materials tested thus far, the optimum frequency was found to be about 1.2 MC.

FIGURE VII. *Equation #3*

$$P_H = \alpha f H_{max}{}^5$$

where

α = hysteresis constant
f = frequency in cycles
H_{max} = max. field strength

One of the most promising materials tested to date is a magnetic form of iron oxide with a chemical composition of Fe_2O_3. The material is prepared by oxidizing pentacarbonyl iron under conditions involving a purification process. The material is then densified to a bulk density of .88 Gm./cc. The particle size, measured with an electron microscope, is between .02–.1 micron.

Figures VIII and IX show the heating rate of this material in distilled water at 1.2 and 2.0 MC at two different magnetic field strengths. Included in these figures are curves showing the comparative heating rate of 20 cc. of beef liver free of iron particles. This shows the excellent temperature differential which can be obtained between the tissue heating and the iron oxide heating. Figure X indicates the rate at which the hysteresis loss increases as the field strength is increased. Equation 3 (Fig. VII) is derived empirically from this data. This

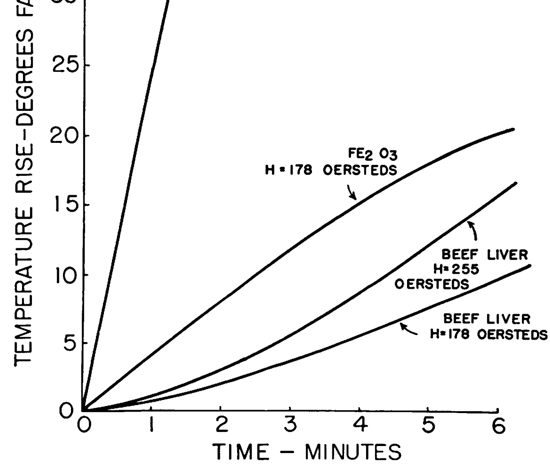

FIG. VIII. Comparative heating rates of iron oxide and beef liver at 1.2 MC.

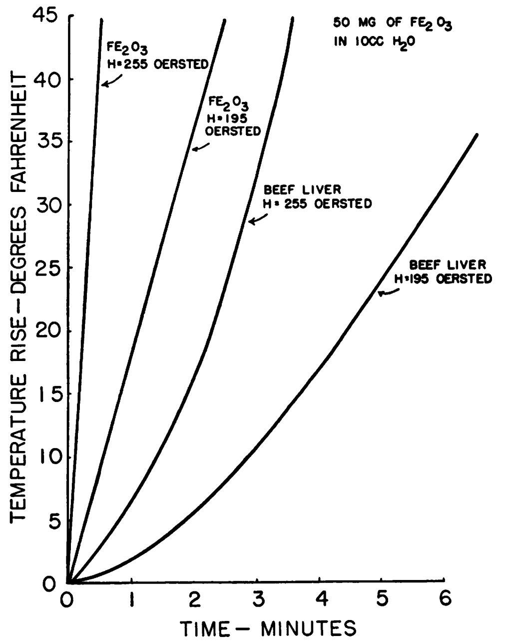

FIG. IX. Comparative heating rates of iron oxide and beef liver at 2.0 MC.

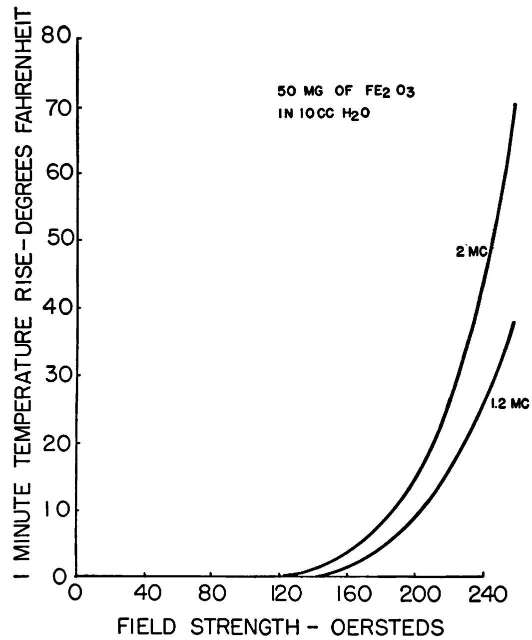

FIG. X. Variation of hysteresis loss with field strength.

relationship is only accurate in the range up to about 300 oersteds as the curves will tend to level off at much higher field strengths.

The early work involving selection of magnetic material and operating frequency was performed with an R. F. generator capable of producing about 1,500 watts of power. With this equipment, it was possible to obtain field intensities of 180 oersteds in a coil 2½ inches in diameter. Due to electrical resistance of the coil, more than 90 per cent of this power is lost as heat which is dissipated by water cooling.

The field intensity is calculated from the geometry of the coil and the relationship (Fig. XI).

This coil provided sufficient work area for the heating of small samples, but was unsatisfactory for experimental work with live animals. A new R. F. generator was designed and built by the Rauland-Borg Corporation capable of producing 12,000 watts of power. The work coil provided for use with this equipment had an inside diameter of 6½ inches and consisted of 6½ turns of copper tubing. Some problems of dielectric heating of tissue have been encountered at the high voltages developed across the larger work coil. This has required the design and development of new and improved work coils.

A further study is being conducted with other powdered materials which exhibit higher coercive force. These materials indi-

FIGURE XI. *Equation #4*

$$H_0 = \frac{2\pi NI}{\sqrt{R^2 + \frac{l^2}{4}}}$$

where

H_0 = field intensity in oersteds at the center of the coil
N = number of turns
I = peak current
R = radius of the coil in centimeters
l = length of the coil in centimeters

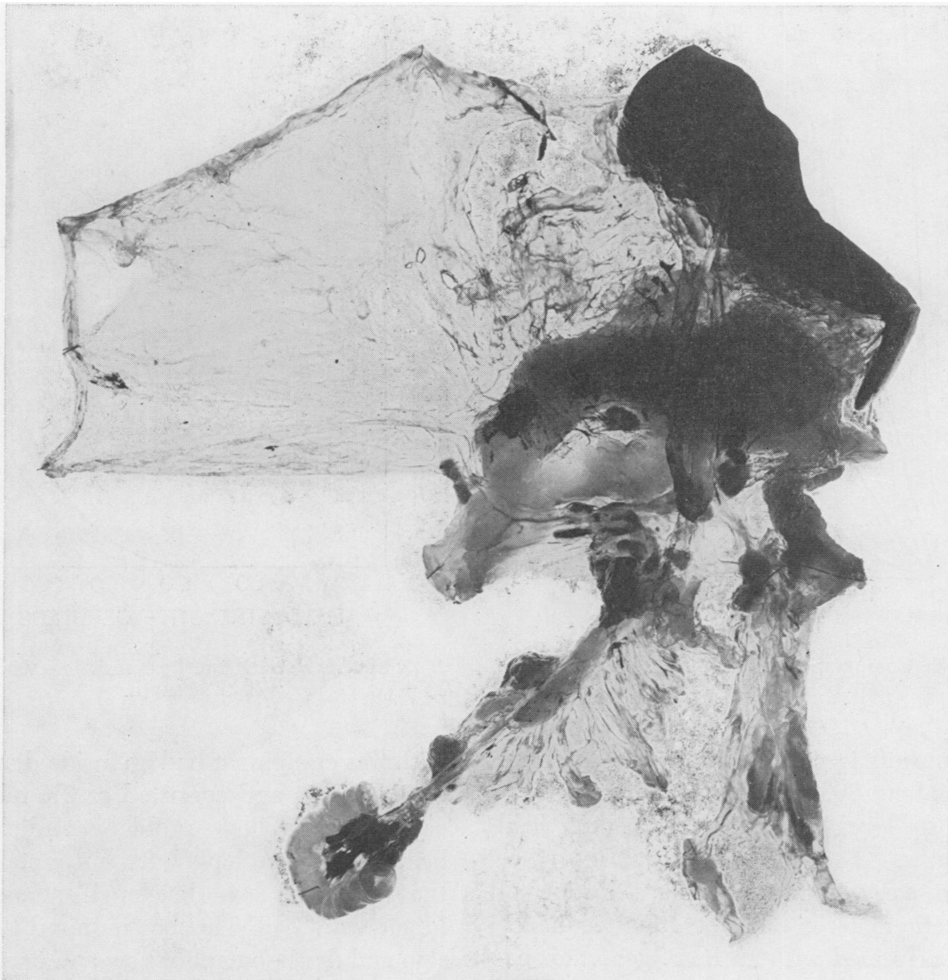

FIG. XII. Cleared specimen prior to dissection of lymph nodes.

cate the possibility of using a much lower operating frequency at a higher magnetic field strength. The lower frequency will permit the use of magnetic structures which will shape the field more efficiently; thereby reducing the input power requirements.

In numerous 10- to 15-kilo dogs, it was determined that iron .02 to .1 micron could be injected into the subserosa, subcutaneous and subperitoneal tissues and from these the particles were carried into the lymph nodes. The injected area and lymphatic drainage area were removed en bloc to include the retroperitoneal area and the aorta and vena cava to the level of the heart (Fig. XII). The nodes were dissected and numbered after the tissues were cleared. Sections (Fig. XIII) were made and sectioned and stained with H and E and Prussian blue. Figure XIV shows the injection site in the subserosa of the bowel. Figure XV shows the distribution of the magnetic iron oxide in a node. Microscopic sections showed no tissue reaction to the Fe_2O_3 (Fig. XVI). These nodes were then analyzed for total Fe_2O_3 content as Fe. Figure

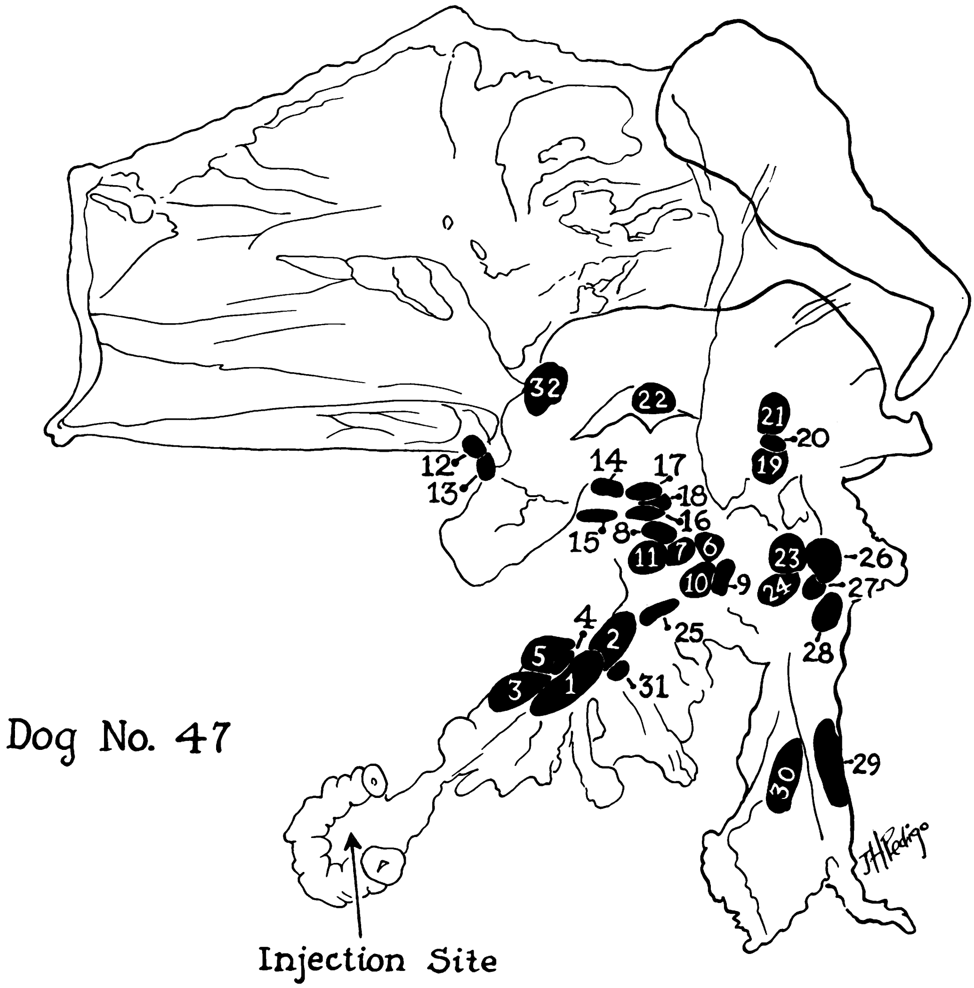

FIG. XIII. Drawing showing location of dissected lymph nodes.

XVII shows the results in dog 47 in mgm. weights and in weights of Fe per gram of node tissue. From experiments *in vitro,* with a field strength of 200 to 240 oersteds, 5 mgm. of Fe_2O_3 per gram of lymph node gave a 14° C. rise of temperature in three minutes. With the new material just now available to us, more iron probably can be injected and a greater rise of temperature can be expected with a smaller field strength.

Temperature changes in tissues have been measured with alcohol thermometers. The alcohol thermometers are too large for live animal work. We are now perfecting a liquid gas phase thermometer. Fine plastic tubes are placed in the tissues to be tested. These tubes are less than .1 cm. in external diameter. They are partially filled with a liquid having a critical temperature near 98° F. A strain gage is used to measure the change of pressure accompanying the temperature change. This is fairly constant over a range of 30 to 50° F. and can

FIG. XIV. Photomicrograph showing injection site in bowel wall.

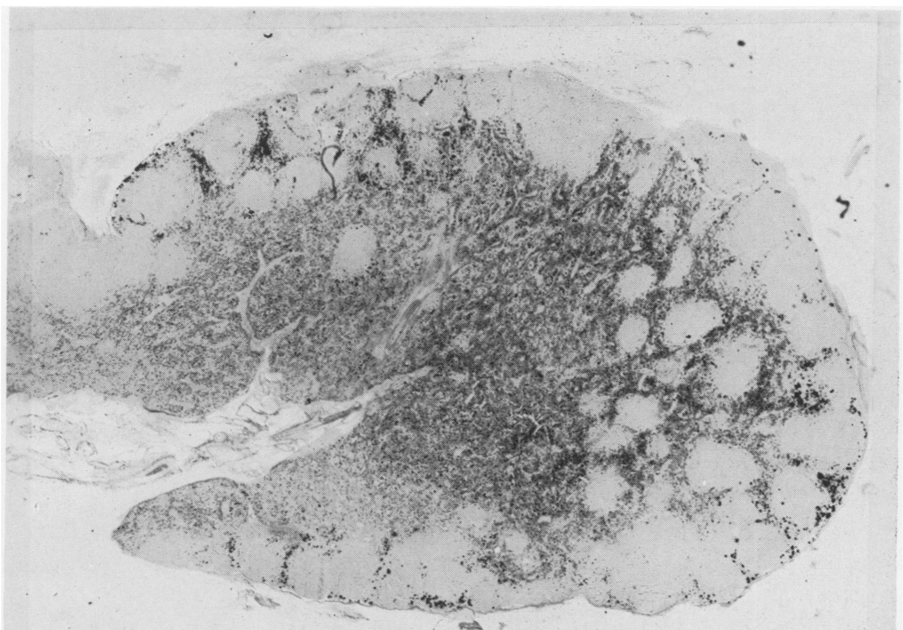

FIG. XV. Photomicrograph stained with prussian blue showing distribution of iron in lymph node.

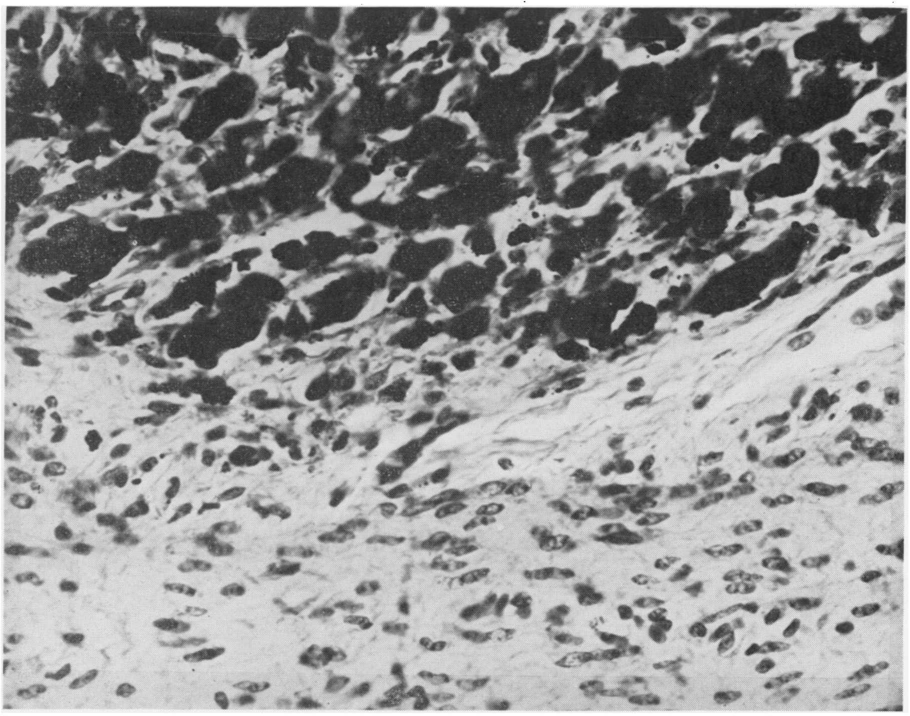

FIG. XVI. Photomicrograph showing absence of local reaction at injected site.

FIGURE XVII. *Summary of Analysis of Nodes from Dog #47 in mgs. of Iron per Gr. of Lymph Node Tissue and Predicted Response*

Mg. Fe/G. Tissue	No.	Predicted Response
(10>)	4	Excellent
(5>)	3	Good
(2>)	9	Fair
(<2)	11	Poor

be used as a thermometer as suggested by Mr. Earle Ballantine. This system is not affected by the electromagnetic field.

We have found that there may be marked heating of surgical steel wire sutures in tissues when placed in such fields. Orientation of the suture loops with reference to the work coil markedly influences this effect. This danger of unintentional heating makes it imperative that any patient who may eventually be treated in this way must not have wire sutures, broken needles or other metallic particles within the area to be treated.

CONCLUSIONS

1. In supposedly curable cancer, detailed studies of lymphatic metastases showed that remaining nodes containing cancer were close to the margin of incision and these nodes were only partially involved with cancer.

2. When injections of particulate matter were made into the lymphatics about tumors in man, it was possible to fill the normal parts of the node with particles one micron or less in diameter.

3. These studies show that it is possible to obtain appreciable differential heating of nodes containing 5 mg. of selected Fe_2O_3 per one gram of tissue. This heating is dependent on the radio frequency, on the

magnetic field strength and on the coercive force of the magnetic particles.

4. Satisfactory amounts of this Fe_2O_3 have been injected into the lymph nodes of experimental animals.

5. All of our findings indicate that we will be able to inject sufficient amounts of recently available magnetic metallic particles into nodes in man. The improved magnetic characteristics and the smaller size of these metallic particles plus an improved type of coil now under construction should give us sufficient heat differential to attain any thermal effect desired in the lymph nodes.

6. When perfected, this system should make it possible to raise the temperature of any part of the body for either a few seconds or for prolonged periods. The possible application of such a tool in the investigation of numerous problems of growth or physiology requires little imagination.

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Discussion

Dr. Harkins: I think this work of Dr. Gilchrist's is outstanding, not only regarding its fundamental importance as an extremely original research contribution, but also with regard to its future practical implications. Even though I am not fully conversant with this type of work, I can't let this excellent paper go by without a brief comment. I think Dr. Gilchrist is to be congratulated on his outstanding work. (Applause)

Dr. Gilchrist: Thank you, Dr. Cope. I have only one thing to say. I would like to thank a great number of people who have helped in this research. Dr. David, when it was first presented to him, encouraged me to continue, though I'm quite sure he thought we would never come to a spot where we could ever say anything about it. But he certainly bore with me.

Secondly, I would like to thank a long-time friend of mine, an electronics engineer, Earl Ballantine, now of Portuguese Bend, California, who, when it was first presented to him, pulled out his pencil and paper and said, "This is the way this will work, and there is no question in the world but what this can be done. It's only a matter of whether you can get someone to make these metals fine enough for you, and secondly, someone who will make the field."

Thirdly, the man who has made this possible refused to let me use his name, but I can assure you that most of this work is not done by medical people.

Fourth, we have an innumerable number of people who have given a good deal of thought and materials to encourage us, most of which have been used in one way or another.

To me, one of the most interesting things has been to see that when you can present a problem in the proper way to people who have skills in industry, they are willing to help you, but our difficulty is that we have a hard time making ourselves understood, since we do not use the same technical terms. I thank you. (Applause)