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THE LIVER AS A SITE AND SOURCE OF CANCER*

BY

G. R. CAMERON, D.Sc., M.B., F.R.C.P., F.R.S.

Professor of Morbid Anatomy, University College Hospital Medical School; Pathologist, University College Hospital, London

The subject of my lecture may well seem to you to be ill chosen, since primary cancer of the liver is uncommon in this country and secondary carcinoma presents few problems to the clinician because of its ill omen as the harbinger of death. My excuse lies in the belief that both the natural history and the experimental study of liver cancer afford precise information from which we may derive hints about the cancerous state and thereby acquire some guidance in the planning of future work.

With the idea of orientating myself to the pathological aspects of the discussion I asked two of my research colleagues, Dr. V. Udall and Dr. Basu Mallick, to analyse the post-mortem records of University College Hospital over the last twenty years for the occurrence and distribution of cancer metastases. During this period it is safe to say that necropsies have been performed with standardized technique, that the type of case admitted to our hospital has not varied greatly, apart from some disequilibrium during the earlier war years, and that careful microscopical search of the main tissues in all instances has been steadily maintained. The results are given in Tables I and II.

TABLE I.—*Metastases in Liver and Lungs Grouped According to Relation of Primaries to Circulation. 910 Cancers from 6,047 Necropsies at U.C.H. over 20 Years*

Site of Primary Cancer	No. of Primary Cancers	Percentage Showing Metastases in	
		Lungs	Liver
<i>Blood Flow Passes to Lungs First</i>			
Breast	49	45	64
Uterus	37	11	24
Ovary	27	11	48
Kidney	19	31	40
Thyroid	10	70	20
Prostate	23	17	9
<i>Blood Flow Passes to Liver First</i>			
Lung	302	—	38
Stomach	144	15	68
Large intestine ..	129	12	40
Pancreas	48	15	58
Gall-bladder and bile ducts ..	31	19	45
Small intestine ..	6	—	33

They show that, whatever may be the immediate relationship of a primary tumour to the systemic or portal circulation, the liver becomes involved in secondary spread in a high proportion of cases. With cancer of the portal tract hepatic metastases regularly and convincingly outnumber secondaries within the lungs. The position with cancers elsewhere, with a

TABLE II.—*Distribution of Metastases from Cancer of Alimentary Canal and from Cancer of Lung*

Metastases in	Cancer of A.C. (290)		Cancer of Lungs (302)	
	No. of Cases	%	No. of Cases	%
Liver	136	48	114	38
Adrenals	5	2	115	38
Brain	—	—	56	19
Kidneys	—	—	42	14
Bone	9	3	37	12
Pleura	8	3	24	8
Pericardium ..	3	1	18	6
Pancreas	26	9	16	5
Spleen	5	2	11	4
Peritoneum ..	49	17	8	3
Lung	38	14	—	—

All other organs under 1% for metastases.

venous blood flow in the first instance to the lungs, is paradoxical. Indeed, in many cases metastases are less frequent in the lungs, where they would have been expected, than in the liver. In other cases, however, lung dissemination predominates over liver. We are thus confronted, at the very outset, with observations suggesting that the liver occupies a special place in the order of metastasis. It will be my endeavour to find out what lies behind this arresting fact.

Sooner or later all pathologists interested in cancer realize the limitations of human studies, and some of them turn to experiments on animals in the hope of achieving a more dynamic and perhaps direct attack on the problem. Since everyone does not agree about the value of animal studies it is worth while considering for a few moments some of the reasons given by cancer workers for this choice.

In the first place, they are quite sure that cancer behaves in animals in much the same fashion as in man, so that some, at least, of the lessons learnt from animal work may be applied with safety to human affairs. Secondly, it is possible to plan experiments whereby the fate of the main tumour or its metastases is influenced by treatment of various kinds. Another matter of some practical importance is the decision whether manipulations adopted during physical examination or surgical operation on the primary tumour increase or diminish the incidence of metastases. This concern certainly lies open to experimental test. Again, they would like to know if there are rules of behaviour shared by metastases and the parent tumour: here may be considered the possibility of an association between the type of tumour on the one hand and its speed of growth, resistance to local conditions, susceptibility to treatment with radiation or operation, and the likelihood of dissemination on the other. Into this category comes, too, the urgent question whether parent tumours

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control the life of daughter tumours. And, finally, they wish to understand why certain tissues of the body are picked out with regularity or frequency by metastases. No doubt other equally good reasons could be added to the list, but I am sure you will agree that I have defined a programme which must convince any reasonable person of the need for experiments on cancer.

Without any more ado I shall pass to the experimental study of metastasis, especially as it concerns the liver, and endeavour to show you that progress is being achieved in this fascinating field of endeavour.

1. Invasion of Blood and Lymph Vessels by Cancer Cells

The first and most important step leading to the distant spread of a malignant tumour is invasion or infiltration of a blood or lymph vessel, the natural precursor to the process of embolism. Growth by contiguity may result in invasion of near-by tissues, and if this form of spread is ignored or defences fail there may be infiltration over an extensive territory. In no such case, however, can there be involvement of a far-distant organ; some motive force is necessary for the carriage of malignant cells to the new site of growth. Morbid histologists have long been aware of intrusion into blood and lymph vessels, for by means of serial sections cells can be traced from the outskirts of a tumour along more or less pliant and yielding tissue spaces to the environs of all kinds of vessels. Indeed, in some instances they have been followed through the wall of such vessels to the endothelial lining, where they have been caught in the very act of bursting through this limiting cellular membrane into the fluid contained within the tube. Histologists also recognize a not infrequent precursor of break-through in the form of thrombosis, which for a time seems to hold up the further progress of malignant cells. But all too frequently it encourages distant spread, since such a thrombus may be the breeding ground of tumour cells until it becomes overweighted and snaps off as an embolus. In this way a small mass of living tumour cells can be whisked away if the near-by circulation is still brisk, and the embolus is finally brought to rest where the blood stream is narrowed down to a set of capillaries with diameters smaller than the largest dimensions of the embolus.

But how do such tumour cells progress from their site of origin to vessels? Once again histologists have helped us by tracing columns or sheets of cells between the two focal points. However, this is not always possible, and we have to fall back upon the supposition that tumour cells possess powers of movement whereby they may cover not inconsiderable distances. Indeed; experimentalists have given us evidence of such motility. As long ago as 1863 the great German pathologist Rudolf Virchow stated that cancer cells as well as leucocytes dodge about like amoebae, and many tissue culturists have confirmed this observation (Carrel and Burrows, 1911; Lambert, 1916; Russell and Bland, 1933; Ludford, 1934). This movement actually has been photographed with the cin camera, and the speed of movement calculated in some cases.

Enterline and Coman (1950) give average velocities for breast cancer cells of 0.7μ per minute, or about 1 in. (2.5 cm.) in 10 hours, for carcinoma of the kidney up to 4.4μ per minute, and for a mouse fibrosarcoma as high as 6.2μ per minute. They have also observed that tiny clumps of carcinoma cells can move about as an amoeboid unit, in a fashion which recalls the astonishing progression of bacterial colonies studied some years ago by Cruickshank. Coman (1944) and his associates (de Long *et al.*, 1950; McCutcheon *et al.*, 1948) make out a case for the importance of adhesiveness between tumour cells in deciding infiltration. Break-away of single cells or tiny clusters of cells depends upon reduction of adhesiveness, which seems to be related in some fashion to deficiency in calcium content of the cells, particularly of their membranes. Here is a field of investigation for the biologist which is certainly related to the fundamental one of movement of cells in general.

The migration of tumour cells in living tissues now can be watched and photographed by means of ingenious techniques, chief among which is the Clark-Sandison and Algire chambers, applicable to the rabbit and the mouse. Before long it should be possible, by their use, to define with precision the factors which favour or prevent the local spread of neoplasms.

2. Carriage of Tumour Emboli in the Blood and Lymph Streams

The demonstration of tumour emboli within the circulating blood or lymph is the next step in the build-up of a theory of metastasis. It has presented many difficulties, since the perceptible growth of even the most active malignant tumour takes many days, weeks, or months, and, so far as we can tell, discharge of tumour cells into vessels is haphazard and on a relatively minute scale. To obtain samples of blood in which tumour cells are demonstrable is a matter of chance, with the odds well against the observer who aims at positive evidence. Success has come the way of several workers who injected blood from tumour-bearing animals into members of the same species (rats, mice especially) and obtained new tumours of the same type at the sites of injection (Blumenthal, 1929; Jonescu, 1931; Gross, 1932). In this way Flaks (1932) confirmed the presence of living tumour cells in lymph nodes receiving the lymph from a sarcomatous area, and could show that such cells were present in the lungs of the affected animals before metastases had made themselves known to the naked eye. From a careful study and review of the subject by Wagner (1938), it appears that the transfer to animals of tumour cells by the injection of heart blood or extract of lung vessels is successful only when such cells are demonstrable microscopically in these fluids. I can recall the excitement that I experienced as a young man when I found cancer cells in smears made from centrifuged blood obtained from a man with a rapidly spreading melanotic carcinoma.

We have no information about the number of tumour cells that must enter the blood of human beings, for instance, in order to produce metastases, but if facts obtained from animal experiments are applicable to man, then the effective number may not be very large. Kahn and Furth (1938) were able to transmit to inbred strains of mice a sarcoma, induced by the carcinogen benzpyrene, with 50 cells. Even more astonishing is the claim of these workers that certain strains of mouse leukaemia can be propagated by injection of a single leukaemic leucocyte into a vein. Obviously many variables come into the story, and a great deal will depend on the growth potentialities and resistance to changed conditions possessed by the tumour cells. Here again is a promising topic for investigation.

We do not know whether metastasis requires the continuous invasion of the blood or lymph stream by small or large numbers of tumour cells or whether discontinuous showers of cells suffice, provided conditions for survival and new growth of the metastasizing cells in their new surroundings are suitable. Some experiments on the influence of massage suggest that the cascading of cells may be important. In Japanese waltzing mice inoculated subcutaneously with a mouse carcinoma by Tytzer (1913) manipulation and massage of the implanted tumour for a short period over several consecutive days increased the speed with which lung secondaries developed, and in some experiments greatly increased the number of metastases in that organ. These experiments were carefully controlled. Confirmation of Tytzer's experiments has come from Knox (1921, 1922) and Marsh (1927). We may well believe that the periods of rough handling of these tumours led to vascular invasion on a scale sufficient to induce successful implantation in distant organs. So, too, experiments on incision or partial removal of primary tumours (Clunet, 1910; Tytzer, 1913) and on the increase of susceptibility induced by haemorrhage (Gaylord and Simpson, 1916) hint at the same sort of phenomenon, although the results are not so convincing as with massage. I agree very strongly with Professor R. A. Willis in his plea for careful experiments on this and allied matters.

But the most persuasive evidence comes from the demonstration (1) that deliberate inoculation of the circulating blood with living tumour cells is often followed by the manifestation of tumours of the same type in various organs of the inoculated animal, and (2) of the need for a break-through into the blood stream of cells from the primary tumour. In support of the first thesis we have the old experiments of Cohnheim and Maas (1877), which showed that finely minced periosteum from rabbits, dogs, and hens injected into the jugular vein lodges as emboli in the lungs and for a time grows there, only to disappear in a few weeks. Cohnheim saw in these observations support for the origin of cancer metastases. Some years later Levin and Sittenfeld (1910) and Gussio (1912) carried out with increasing care, as the pitfalls were realized, inoculation experiments which gave convincing support to the embolic theory of secondaries. Modern work has confirmed the pioneers' results. Even more illuminating are the experiments of Weil (1913) with the Flexner-Jobling rat sarcoma. This actively growing neoplasm can be transmitted from one animal to another by means of subcutaneous inoculation but fails to metastasize spontaneously. If suitable emulsions of the sarcoma be injected intravenously into rats with large subcutaneous tumours then a high proportion of these animals develop lung tumours. In other words, when tumour cells gain access to the veins of tumour-bearing animals metastasis follows. Weil concluded that the absence of spontaneous secondaries is due to failure of the primary growth to effect vascular invasion. We now know that this is an over-simplification of the story; nevertheless blood invasion is indispensable if a tumour is to spread to distant parts.

3. The Development of Metastases

For the development of metastases in an organ such as the liver there must be: (1) the impaction of living tumour cells within the blood vessels, especially the capillaries, of that organ; (2) the initiation of a new focus of tumour growth at the site of impaction; (3) the invasion of the perivascular tissues of the organ by new tumour cells breaking through impacted vessels. Each of these stages has been established by means of animal experiments, and there is equally impressive evidence from human experience.

The frequent impaction of tumour cells in various organs, especially the lungs, was convincingly established by Schmidt (1903) and confirmed by a host of pathologists. In the course of a careful microscopical study of 45 cases of abdominal cancer he found 15 with lungs either free from metastases or showing at the most minute white rice-shaped thickenings, which proved on microscopical examination to be blood vessels obstructed with cancer cells. In all such cases small collections of tumour cells were discovered within the smallest arteries or in the capillaries, either free or enclosed within thrombi. Some of these collections displayed indistinct broken-up nuclei and fused, homogeneous, poorly stained masses of cytoplasm—signs that the cells no longer survived. Others presented mitotic figures and were certainly growing. Occasionally tumour cells entirely filled vessel lumina and formed long columns extending from arteries to capillaries and even to veins. Spread through vessels to perivascular tissues could also be made out and from these areas could be traced the origins of true metastases. Schmidt concluded that the transportation of tumour cells to small lung arteries occurs with great frequency, but that only a small proportion of these passengers are transformed into secondaries. The bulk are killed off by encapsulation with red corpuscles and leucocytes or by the organization of the thrombi which rapidly enclose them.

I would repeat that the studies of Schmidt are exemplary and have never been surpassed. Though chiefly concerned with tumour emboli in the lungs they are applicable to other organs, with certain slight reservations. In the case of the liver, for instance, it is my experience that thrombi around impacted tumour masses are by no means common—an event not altogether unexpected when one recalls the part played by the liver in the prevention of blood coagulation

by its synthesis of heparin. As an instance of the extraordinary fashion in which tumour cells may grow within blood vessels before breaking through the endothelial barrier let me recall a case described by the Canadian pathologist Horst Oertel (1935). A primary pyloric carcinoma came to necropsy without any obvious signs of metastases. Many organs, but especially the liver and the lungs and to a less extent the right adrenal, bone marrow, and bodies of some dorsal vertebrae, and the dura mater, showed widespread microscopical cancerous masses confined wholly to the blood vessels. The tumour cells had been growing alongside the circulating blood in these localities without displaying any aggressive tendencies for the closely associated tissues.

A further instance of the same sort of event, but this time deliberately induced in animals, are the experiments of the Japanese investigator Takahashi (1915-16) carried out at the Imperial Cancer Research Laboratories, London, during the first world war. White mice were inoculated intravenously with 0.2 g. suspension of various mouse tumours and killed after the lapse of three weeks. In a number of animals no tumours were found within the lungs despite most careful search, but tumour emboli in various stages of degeneration and thrombosis were numerous. Leucocytes were present in considerable numbers around the tumour cells, but the endothelium of the enclosing blood vessels showed no evidence of proliferation. In those mice with lung secondaries after intravenous inoculation, degeneration was certainly not obvious in the tumour emboli and signs of tumour proliferation became apparent after three days. Both carcinoma and sarcoma were equally capable of producing lung metastases, but tumour strains differed widely in their ability to survive intravenous implantation. The majority of the strains used in these experiments grew when inoculated subcutaneously, but no relation existed between success on subcutaneous implantation and tumour take in viscera after intravenous injection. Takahashi concluded that variation in production of metastases is not so much the failure of neoplastic cells to make their way into the blood stream as their inability to survive and grow after arrest in the vessels of an organ.

Modern studies of dissemination in general are worth noticing before we consider special problems of liver metastasis. American investigators have been particularly active in recent years in the design of quantitative studies. Fresh confirmation has come for the belief that the number of emboli reaching a tissue is important in determining the success or failure of spread. Since the mortality of embolic cells is very high, a great number of these cells fail to establish themselves in the organs preliminary to initiating a locus of growth (Warren and Gates, 1936; Zeidman *et al.*, 1950). Zeidman *et al.* determined the number of living cells by means of vital staining with trypan blue, in suspensions of mouse sarcoma, injected such suspensions in serial dilutions intravenously into mice, and counted the pulmonary tumours 18 days later. Table III shows that the number of metastases is directly proportional to the number of viable embolic cells.

These investigators, too, maintain that the number of metastases is proportional to the duration of the primary growth; the longer the primary tumour exists, the greater is the number of metastases. This is not a matter of chance of invading blood vessels, for there is no reason to believe that the final size—that is, the amount—of a primary tumour is a measure of the likelihood of metastasis. Such factors as motility of cancer cells and their power of destroying and overcoming natural defences must play an important part,

TABLE III.—*The Number of Metastases is Directly Proportional to the Number of Viable Embolic Tumour Cells. Mouse Sarcoma (Zeidman *et al.*)*

No. of Mice	No. of Viable Cells Injected Intravenously	Average No. of Pulmonary Tumours
10	104,400	11.5
10	19,800	2.5
8	5,400	1.7
10	900	0.3

but so far no quantitative methods have been invented for testing these propositions. I believe that this kind of investigation would give valuable returns.

4. The Liver as a Site of Metastasis

I must now turn from my general discussion of metastasis to consider the special problems of liver involvement.

Let me remind you, first of all, of the more obvious mechanical factors which contribute to the formation of secondaries in this organ. If cells from the parent tumour reach the portal blood then they will behave as emboli which lodge in the smallest portal venous radicles within Glisson's capsule or, if very small, they may even penetrate the liver lobules before coming to rest within the sinusoids. Since there is a rich anastomosis between the lobular sinusoids block is not a serious matter, and cancer emboli are unlikely to experience oxygen deficiency from purely mechanical reasons. Indeed, many observers have commented upon the ease with which these cancer cells grow and spread, sometimes for considerable distances. Moreover, they seem to seek out fresh and larger venous channels, as Willis reminds us. Each new break-through adds further opportunities of spread and encourages new cycles of growth. The risk of cells being carried away from the liver to the lungs by the hepatic venous blood has also to be faced and sometimes the lymphatics are also concerned in spread. Metastasis to the liver thus is fraught with great potentialities for catastrophe.

Investigation of the hepatic circulation has brought to light two strange properties which must be taken into consideration. For some years now we have gradually become aware of the importance of streamlining in the flow of liquids and gases. Flow of blood in the portal vein of animals is certainly streamlined, and it appears that portal blood from the stomach and spleen passes to the left portion of the liver and that from the greater part of the intestines is directed to the right half of the organ (Copher and Dick, 1928). Whether these rules can be applied to man seems doubtful if one considers the distribution of secondaries in the liver. Walther's and our experience engenders no enthusiasm for the view, although it is true that one sees specimens from time to time which suggest the influence of streamlining on distribution. More careful studies are badly needed before we can finally assess the position.

The second feature that cannot be ignored is the existence of territorial peculiarities in the blood flow through the liver and the presence of arteriovenous anastomoses. The former have been established in some laboratory animals by Daniel and Prichard (1951) by the use of cinephotography. These workers have demonstrated curious channels of direct flow from hilum to hepatic vein and have studied some of the factors which modify them. What part they may play in metastasis can only be guessed at. Arteriovenous anastomoses still have to be established in the human liver, but there is little doubt about their existence in some animals. Wakim and Mann (1942) and Seneviratne (1949-50) have found them in the transilluminated liver of the rat and mouse. Prinzmetal and his co-workers (1948) have shown that minute glass spheres up to 150 μ diameter can pass through the liver when they are introduced into the portal vein and be recovered from the lungs. Dr. Basu Mallick has confirmed these observations in my department. It is tempting to conclude that this phenomenon explains the absence or paucity of metastases in the liver that puzzles the pathologist from time to time when the lungs and other organs are the sites of secondaries.

But whatever may be the outcome of this kind of investigation all of us who have kept records of the distribution of tumours agree that the liver is an organ with some kind of predisposition for secondary carcinoma. From Table I emerges the fact that primary cancers make a habit of involving that organ, no matter what may be their relationship to the systemic and portal circulations. Nearly 70 years ago Stephen Paget (1889), in recording 735 fatal cases of carcinoma of the breast in which necropsy had been per-

formed, noted that the liver was the seat of secondaries in 241 cases, whereas the lungs were involved in about 70, the kidneys or suprarenals in 30, and the spleen in only 17 instances. For this and various other reasons he adopted the idea put forward some years previously by Langenbeck, in Germany, of cancer cells requiring congenial soil if they are to live and grow. The "soil" idea, as a first approximation, ought to be a profitable hypothesis for further investigation, but it must be reluctantly confessed that it has led to little action though much speculation (Willis, 1952; Coman, 1953). I would like to direct your attention to several experimental studies which I think are full of interesting suggestions.

Some Experimental Studies

In 1932, Foulds, of the Imperial Cancer Research Fund, London, found that 92 rabbits with intramuscular implantations of Brown-Pearce tumour had developed secondaries in 25 instances. The adrenals were involved in 16, the kidneys in 14, the eyes in 11, the liver in 3, and the lungs in 2 animals. Intravenous inoculation of 71 rabbits with suspensions of this tumour resulted in embolic tumours in 60 animals, the growths being most frequent in the kidneys, adrenals, and eyes, and less frequent in the liver and lungs. When 34 rabbits were vitally stained with trypan blue before intravenous inoculation with the tumour suspension, growths were obtained in 30 animals, 17 of which showed splenic tumours. This was a surprising result, since at no time were tumours encountered in the spleens of unstained rabbits. By means of vital staining, therefore, Foulds had depressed the resistance of the spleen to tumour growth, and the organ now became a suitable "soil" for the ripening of the seed. Naturally enough, he suggested that the reticulo-endothelial elements might be the cellular basis of this splenic resistance, and it is not unreasonable to conjecture that these cells are concerned—as they are with resistance to many infective agents—with cancer resistance in general.

The likelihood of a cellular factor in resistance recalls the older experiments of Jones and Rous (1914), who showed that, by stimulating mechanically the peritoneum of mice by injections of kieselguhr, the growth of inoculated tumour can be encouraged at such points of irritation, for cells are quickly supported and nourished where a very cellular connective tissue is induced by the irritant. Here we are dealing with a phenomenon which may be allied to that recognized by Schmidt in the growth of metastases, but, taken in conjunction with Foulds's results, it suggests a dual mechanism of resistance to, and support for, cancer cell growth.

The "Soil" Hypothesis

Highly significant experiments planned to test the soil hypothesis have been carried out by Coman *et al.* (1949). A squamous-celled carcinoma of domestic rabbits—labelled V₂—has been discovered which disseminates regularly to adjacent lymph nodes, occasionally to the lungs, but rarely elsewhere. If suspensions of this tumour are injected intravenously, extensive cancerous infiltration of the leg muscles often develops thereafter in 65-86 days. It would seem that if large numbers of V₂ cells are able to reach the muscles they have no difficulty in establishing themselves there and producing secondaries. Yet observations on natural spread encourage the idea that muscle is an unfavourable soil for this tumour.

Again, if cancer cells from V₂ are injected into the left side of the heart they produce metastases everywhere. Apparently when these cells reach the left side of the heart in any number they will induce secondaries in any kind of tissue. In other words, they must first escape being trapped in the lungs, for even heavy suspensions of tumour cells injected into the right heart or femoral vein fail to give metastases elsewhere than in the lungs. These interesting experiments show the need for assessing the value of protective and mechanical factors before resorting to hypothetical explanations. However, this is not all of the story, for there are tumours such as the Brown-Pearce carcinoma of the rabbit, whose cells can pass through the pulmonary

labyrinth without delay, producing widespread visceral metastases, among which liver secondaries stand high. Arteriovenous anastomoses in the lungs (Prinzmetal *et al.*, 1948) no doubt would afford a rational basis for these results, but such anastomoses cannot explain why some tumours pass through rapidly and others not at all. Here is a further problem for study.

Finally, allow me to mention the experiment of Lucké *et al.* (1952), in which living V_2 carcinoma cells were injected simultaneously into the afferent blood vessels of the liver and the lungs of separate groups of rabbits in order to ascertain whether the resulting tumours grew equally well in these organs. In all of the 25 animals that were suitable for comparison the mean size of liver tumours exceeded that of lung tumours, whether the liver had been injected through the portal vein or the hepatic artery. Twelve days after the inoculation the liver tumours were about five times greater in volume than the corresponding lung growths, and after 35 days liver tumours were 100–250 times greater in size than those in the lungs. Lucké *et al.* conclude that tumours, once established, grow faster in the liver than in the lung, and they maintain that the liver is a better environment for supporting tumour growth than the lung. They obtained further support for this idea from 154 human necropsies, and with this reassurance they returned to the view that tissue environment or “soil” is of importance for metastasis. Coman (1953) likewise has reached the same conclusion in his most recent survey of the matter. On the other hand, Patey (1936–7) found that the Brown-Pearce carcinoma of the rabbit injected into the portal vein or systemic venous circulation gave many more secondaries in the latter instance than in the former. In neither case were metastases so numerous in the liver as in the kidneys, which appeared to be the most suitable “soil” for this tumour. Once again we find ourselves in the midst of conflict from which there is no escape but to admit the likelihood of a number of factors that condition the behaviour of each tumour.

Clearly it should be my final task to consider, for a few moments, some of the factors that might influence the growth of cancer cells in the liver with the object of defining more precisely the qualities of the hypothetical “soil.” As a guide to this discussion let me postulate what I shall call “the principle of near-equivalence” for primary and secondary tumours. I refer to the necessity for conditions at the site of development of both these types being equivalent or almost equivalent in a strictly denumerable sense. We must be able to match such factors as the need for adequate oxygen supply, nutrition, hormones and vitamins, resistance mechanisms, and perhaps a great many other dimly perceived requirements—for example, Haddow’s hypothetical growth factors—one against the other in considering parent and daughter growths. When this has been agreed upon local differences must surely indicate the predominance of one or other factor at that particular locality or the presence of something outside the group of agencies under consideration. Let us consider for a moment how we stand with some of these comparisons.

At least six notions may be offered in consideration of the liver as soil; some of these have been discussed by Willis (1934, 1948, 1952) and Walther (1948), the authorities on metastasis.

1. Oxygen Supply.—Is the oxygen supply of the liver different from that of other organs in which metastases are infrequent—for example, the spleen—or similar to that in tissues which are common sites for metastases, such as the lungs? Unpublished work in my own department by Dr. R. M. L. Mehrotra has shown the great variability in oxygen uptake in the rabbit’s liver, and this agrees with observations made on the dog’s liver by Blalock. I know of no accurate information about the oxygen uptake in the spleen, which, however, seems to be well off for oxygenated blood and is remarkably intolerant of anoxia. In the lungs, metastases first develop in the arterioles and arteriolar capillaries; the former, at least, contain venous blood. But many instances can be brought forward of the development of metastases in well-oxygenated tissues, so that, on the

whole, the factor of oxygen supply cannot be important in the early stages of spread. Later on, when ischaemia intervenes, we know that growth of tumour cells may be seriously impeded and the cells destroyed.

2. Nutrition.—Willis (1934) has emphasized the rich carbohydrate supply in conjunction with poor oxygenation in the liver and is inclined to believe that these conditions will favour the survival and proliferation of cancer cells. I cannot accept his statement that oxygenation is poor, even though he is correct in pointing out that the hepatic artery is small and blood flow through its medium is restricted. We must take into consideration the part played by portal blood in supply of oxygen to liver cells even though it varies a great deal from one animal to another and from time to time. Nor should we forget that the hepatic artery makes up in speed of flow what it loses in volume. Payling Wright (1950) emphasizes the exceptionally high concentration of amino-acids reaching the liver from the alimentary canal and thinks this may be important in stimulating growth. I know of no experimental evidence that excess of nitrogenous units, or indeed of protein or any other food, stimulates the growth of tumour cells apart from a temporary acceleration. However, a depleted food supply appears to reduce the growth of certain tumours for a time. Of course, there may be qualitative factors which are more important than quantitative, but here again we are on uncertain ground.

3. Defence Mechanisms.—We have already noted a little evidence that reticulo-endothelial cells are important in resisting tumour growth. Unfortunately, no clear correlation between the amount of R.E. tissue and tumour resistance can be made out in such organs as lungs, liver, spleen, lymph nodes—all rich in R.E. cells—and kidneys, brain, bones, rather poorly off for R.E. cells. Perhaps when we know more about the factors that control R.E. cell activity we shall be able to explain resistance better. Such properties as speed of mobilization of cells, their adhesive tendencies—well marked in the case of the Kupffer cells of the liver, according to Rous—and their capacity to produce antibodies and to phagocytose must be of importance in deciding the qualities of soil.

4. Metabolites or secretory products formed in the tissues by tumour cells which may modify tumour growth. Willis (1952) discusses the information we possess about this matter, but it is indeed scanty when we consider organ differences.

5. Humoral defences, such as the local production and storage of antibodies, antibiotics, and the like, about which we can only guess.

6. Competition between the organ parenchymal and stromal cells on the one hand and invading cancer cells on the other. The late Dr. R. H. D. Short, in suggesting this possibility to me, proposed the view that what is left over after parenchymal cells have had their share of oxygen and food may be of vital importance for metastasizing cancer cells. In the later stages the position seems to be reversed, for the normal cells appear to be victims of the secondary tumour, undergoing degeneration and necrosis or atrophy. Stromal cells, in contrast, usually survive, and indeed may proliferate to give the scirrhous reaction.

No doubt other possibilities might be added to this somewhat indeterminate list; some of these I anticipate will be the concern as much of the normal cell and its environment as of the cancer cell. A start has been made in the analysis of variation in reaction to simple injury in tissues, from which has come the idea of fields of differing activity (Cameron and Mehrotra, 1953). Some such method of study might prove of value in the investigation of soil. Indeed, our concept of fields may turn out to be identical with that of soils, but only further research can settle the question.

Conclusion

My survey of the position of the liver in the hierarchy of metastasis has led us through a veritable icefield of disappointments and uncertainties heavily littered with crevasses of ignorance. But we need not

despair, since there is, I believe, a perceptible upward trend in our journey towards the goal of enlightenment. Comfort springs invariably from the labours of defining what we know and what we do not know, and many gloomy fears vanish in facing up to the unknown. My endeavour has been to define some of the problems of tumour spread which I believe would repay further investigation. I would plead, especially, for a change in attitude towards matters which are dismissed as insoluble. Why should we throw aside the problem of metastasis as hopeless? Why not strive to find ways of circumventing the growing tumour, by inhibiting or suppressing its powers of growth, by turning it aside into less innocuous channels, perhaps by throwing obstacles in its pathways of spread or even sacrificing healthy tissues in order to hold up the neoplastic invader by means of a "burnt earth" policy?

The search for effective chemotherapeutic measures must go on with the same enthusiasm and imagination displayed by Dr. Blair-Bell throughout his pioneering efforts in this great city of Liverpool. Ideas must be sought after and cultivated. We must not be afraid to attempt the impossible; no device or technique that holds out the faintest hope of discovery can be put aside without proper reference to the work in hand. Above all, I maintain that we teachers have a special duty to perform in firing the imagination and carefully fanning the flame of enthusiasm so that our young men and women may demand an entrance into the domain of cancer research. Perhaps it will be a supreme, audacious flight of youthful genius that will bring the answer to the riddle of neoplasia.

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TOXIC REACTIONS AFTER INTRAVENOUS SACCHARATED IRON OXIDE IN MAN

SUGGESTIONS FOR IMPROVED PREPARATIONS

BY

J. A. NISSIM, M.D.

(From the Department of Pharmacology, Guy's Hospital Medical School, London)

It is six years since saccharated iron oxide was introduced for intravenous administration in patients refractory to or intolerant of oral iron (Nissim, 1947). Saccharated iron oxide may be said to have gone through the first critical years of its life with greater success than expected, and as regards the incidence of serious reactions following its administration it compares favourably with blood transfusion. Mild or moderate side-effects, however, have been reported rather too frequently. Holt (1953) made a plea for an assessment of the general toxicity of saccharated iron oxide. It is the object of this paper to give an account of my clinical experience with this preparation, albeit limited, and to submit the findings of various authors to careful analysis in the hope of shedding light on the type, incidence, and possible causation of these reactions. This is followed by suggestions of possible procedures to eliminate or minimize the incidence of such reactions.

Toxic Reactions in Animals

Toxicity studies of intravenous saccharated iron oxide in four species—namely, mice, rats, rabbits, and guinea-pigs—have shown conclusively that the observed toxic effects are associated with precipitation (Nissim, 1949, 1953a; Nissim and Robson, 1949). This iron preparation does not precipitate when mixed in any concentration with plasma or blood *in vitro*, but undoubted precipitation occurs *in vivo* above threshold doses, depending on the species. In the mouse and rabbit this threshold is around 45 mg. Fe per kg. body weight, above which gradual precipitation of the compound occurs. The iron precipitates in fine particles rather than clumps as occurs after colloidal ferric hydroxide (Nissim, 1949, 1953b). For this reason the toxic effects of saccharated iron oxide after such doses occur only after an interval when enough iron has precipitated. Precipitation occurs particularly in the lung capillaries.

Plasma iron and histological studies show that at a second and higher threshold—namely, 180 mg. Fe per kg. in the rabbit—saccharated iron oxide is followed by abrupt but partial precipitation, and is therefore capable of producing toxic reactions immediately after the injection of unusually large doses—for example, 360 mg. Fe per kg. The toxic effects are those of multiple embolism. No toxic reactions have been noted which could not be explained on the basis of pulmonary or systemic precipitation.

Types of Toxic Reactions in Man

My experience with saccharated iron oxide includes 28 patients, 19 in the first series (Nissim, 1947) and 9 in the second (Nissim, 1949). The total number of injections was 90, and the dose per injection varied from 10 mg. to 1 g. Fe. Two samples of saccharated iron oxide were used, one with an LD₅₀ in white mice of 180 mg. Fe per kg. body weight, the other with an LD₅₀ of 300 mg. Fe per kg. With the latter sample, which was used in the second series, doses of 200–300 mg. were given on 20 different occasions without toxic reactions of any kind. Only four mild or moderate reactions were encountered, all of which were in