# Section of Urology

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## Malignant Cachexia

PRESIDENT'S ADDRESS

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ABSTRACT.—Well-known authorities such as Ewing and Willis have thrown doubt on the existence of a constitutional effect of malignant disease other than that due to hæmorrhage, infection, mechanical pressure, &c. On the other hand, Greenstein has taken the opposite view and maintains that a local malignant growth has a general constitutional effect.

The clinical picture of malignant cachexia is as clear cut as that, for example, of old age. Malignant cachexia is a recoverable state in certain circumstances when the primary growth is removed; clinical evidence warrants the conclusion that it is a genuine entity and that it is a generalized disease. The laboratory findings have not established that the degree of depression of any one system is the predominant cause of death. Clinically, however, the most deadly effects seem to be those produced on the cardiac and alimentary musculature. Experimental evidence would seem to have shown that there is a specific effect, chiefly on one of the cellular enzymes, catalase, predominantly in the liver but also to a lesser extent in the kidney. There is also a marked effect on the blood-forming organs. Greenstein's view that there is depression of the metabolism of the iron porphyrins naturally attracts our attention. Whether this effect is the result of some substance added to the circulation or taken from the circulation is uncertain, but an additional effect seems most probable.

Tissue culture may enable us to confirm the existence of the metabolite responsible, and perhaps to identify it. The hitherto untreatable anæmia of malignant cachexia gives us another line of investigation.

THE urologist is in a peculiarly fortunate position to study the condition of malignant cachexia, for cancer of the kidney and cancer of the testis frequently cause it in a comparatively uncomplicated form.

We have now reached a stage in the study of malignancy which is interesting and satisfying, satisfying because so much positive knowledge has been accumulated that the possibility of understanding the process is beginning to emerge. To me it seems that we have at least three major problems to solve. The first is: what chemical changes take place in the cell to make it become as we say, malignant, causing it to embark on its course of irreversible division, maintaining itself and largely ceasing to function. The second is: what is the explanation of its other new properties. Why can a neoplasm, for example, metastasize? A split skin graft will not survive unless it is autogenous, and its destruction is thought to be due to antibody formation by the recipient. A malignant growth is almost the only protein complex which can be transplanted into another host without generally evoking a manifest allergic reaction. Again, when the body is injured—for example, when the kidneys are severely bruised or ruptured—it is very likely indeed that cells are displaced into the circulation. Yet there is no very certain evidence on record of metastasis of normal tissue. My colleague, Dr. D. L. Woodhouse (1941, 1953) in the Cancer Research Department of Birmingham University, has carried out some experiments to study this problem, so far, I understand, with negative results. The third problem—which is the subject of my paper—is why does the growth kill the patient.

### THE CLINICAL PICTURE

We are all only too familiar with the clinical picture of malignant cachexia, the unsmiling, wasted face, the somewhat sallow and occasionally anæmic complexion, the languid air, the flaccid dry skin, the complete lack of energy, the loss of appetite, the history of loss of weight, and not infrequently the infection of the mouth with thrush. Strange to say, typical as this picture usually is, with its many positive and also negative features, there are those who deny that it is a real entity, and who insist that the fatal illness from malignancy is due to well-known and obvious defects. A leading exponent of these views is Professor R. A. Willis (1948) who states that the condition is accounted for without postulating toxins or an extravagant nutritional demand by the tumour, and that it is the

result of such factors as starvation, hæmorrhage, ulceration, bacterial infection, destruction of functionally vital tissues e.g. bone-marrow, pain, sleeplessness and anxiety. Ewing (1940) states "our present knowledge derived from careful clinical studies, from observation at autopsy, and finally from chemical investigation, seems to warrant the conclusion that a peculiar toxin secreted by cancer cells and leading to cachexia does not exist".

That certain malignant growths at any rate, give off abnormal substances into the blood stream, is a matter of common knowledge. Four well-known examples are the increased serum acid phosphatase in cancer of the prostate, the Bence-Jones proteinuria in myelomatosis, the excretion of melanin in the urine in some melanotic growths, and disturbance of temperature in tumours, for example, of the kidney, no doubt due to some pyrogen in the circulation. These constitutional effects are, of course, not manifestations of cachexia. They are merely quoted as examples of constitutional effects produced by a localized growth.

In direct opposition to the views of Willis and Ewing, we have those of Greenstein (1947, p. 316) who, in supporting the view that a local growth has a constitutional effect, states that "the unhappily familiar cachexia of patients with advanced neoplastic disease is a clinical symptom of these effects—sometimes considerably exaggerated, sometimes masked as a result of secondary causes . . . but nevertheless fundamentally due to systemic alterations produced by the tumour on the host".

He considers that these effects may be produced either by liberation into the blood stream of material produced by the tumour, or by an abstraction by the tumour of some component in the blood stream essential for the maintenance and proper function of the distant tissues. This opinion is supported by a great deal of experimental information which I shall mention later.

It is clearly of considerable practical importance to decide which of these authorities is right. Is malignant cachexia in the absence of hæmorrhage, ulceration, or a mechanical effect, due to dissemination of the growth with bone-marrow displacement, &c.? If so, it is an indication of inoperability. If, on the other hand, this type of illness can be produced through the blood stream without dissemination of the growth, then clearly it is not an indication of inoperability. Furthermore, though this is, of course, very speculative, if there is a constitutional effect produced through the blood stream by the growth, we might venture to hope to be able to counteract it, perhaps by some medical means, and thereby to improve the quality of the patient's life and perhaps to prolong it, even though we cannot cure him. In this connexion, it is very interesting to note that some cancers do not appear to produce as grave a disturbance of health as others, a good example being cancer of the prostate.

I suppose I might say also that even if a study of the condition leads to no practical results, it is a poorly explored field, investigation of which has an interest of its own.

To help to focus attention on this matter, here are the histories of the following patients seen recently.

*Case I.*—F. J. W., aged 61. First seen in May 1953, with only a three weeks' history of which the first symptom was pain in the loin. This was followed by hæmaturia and, two weeks before admission, by swelling of both legs. Death took place 1.6.53 about six weeks after onset of symptoms.

The post-mortem showed the patient to have a highly anaplastic carcinoma of the kidney. There were secondary deposits in the lung but the liver was free from growth.

*The following are the results of tests taken over one week:*

Blood pressure (12.5.53) 130/80. Blood count: R.B.C. 4,390,000; Hb 90%. Blood urea 32 mg.%. Serum sodium 305 mg.% (133 m.eq/l); serum potassium 22 mg.% (5·65 m.eq/l); serum chloride 360 mg.% (102 m.eq/l).

Plasma $CO_2$ combining power 50 vol.%; plasma pH 7·40.

Liver function tests: Serum albumin 4·5 g./100 ml., serum globulin 2·5 g./100 ml., serum-free cholesterol 92 mg./100 ml., serum ester cholesterol 150 mg./100 ml., serum alkaline phosphatase 11·6 units/100 ml. (Jenner and Kay).

van den Bergh: The direct reaction is negative; the indirect reaction is negative.

Cephalin cholesterol: negative. Thymol turbidity: 0·5 unit. Thymol flocculation: Nil.

Colloidal gold: Patterson: 1; Maclagan: negative.

Urine: sterile.

ECG.—Sinus rhythm, rate 98; rather low voltage of ventricular complexes in limb leads; no other abnormality.

No pyrexia. Temperature reached 99° F. on three occasions. Patient's clinical condition was characterized by wasting and weakness. His mind was not quite clear in the last few days.

The death of this patient within six weeks of the onset of definite symptoms does not seem accountable for on the basis of the views of Willis and Ewing.

*Case II.*—The second patient, P. J. G., aged 68, was investigated by a medical colleague of mine because of general failure of health with loss of weight. Examination on admission to hospital showed a cachectic and anæmic man, the only other positive finding being some occult blood in the stools. He was gastroscoped and it was thought that there was an erosion to be seen on the greater curve of the stomach. A laparotomy was therefore performed by Professor F. A. R. Stammers when it was found that there was no external evidence of a lesion in the stomach and a mass was recognized retroperitoneally in the left renal area. Further investigation showed that there was, on intravenous pyelography, a filling defect on the left side. The blood urea was within normal limits. On 7.1.53 a nephrectomy was done. The kidney was the site of a tumour of uniform yellow appearance which was reported by the pathologist to be a clear-celled carcinoma of the kidney with an unusual amount of fibrous tissue in the stroma. The patient was last seen on 13.7.53 when he was reported to have gained 2 st. in weight.

*Case III.*—J. P., aged 65½. Admitted under Professor W. M. Arnott in September 1948 complaining of frequency and hæmaturia. On examination, he was described as tremulous, weary and miserable. In October 1948, a left lumbar nephrectomy was performed, the kidney containing a tumour 15 × 10 cm., of yellow necrotic appearance, reported to be a Grawitz tumour. Four months later, the patient was reported to be in excellent general condition. However, he died of his disease three years after the operation.

These last two case histories do suggest that removal of the primary neoplasm substantially benefited the patient, at any rate for a time. In Case I (F. J. W.), the cause of the patient's illness to begin with was quite obscure. The last patient evidently was remarkably improved after the removal of the primary tumour. I have not sought to multiply these examples; they are a commonplace experience of all clinicians.

In investigating malignant cachexia, it is first of all worth while considering each main system in the patient. Let me emphasize at once that the patient must be studied well before the terminal phase of the disease. Osler (1917) has pointed out that patients suffering from chronic illness rarely die of the disease which brings them to their death bed. On post-mortem findings alone, paradoxical as it may seem, we would find it difficult to maintain the existence of such an entity as death from old age, and indeed it might seem that old age as a significant cause of death could be largely ruled out on the basis of Professor Willis' list of explanations of death from cancer. Of a total annual death-rate of half a million, the number of deaths from senility recorded in the Registrar-General's reports for 1950 and 1951 are just over 9,000 in each year, yet that senile decay exists is beyond any question, and no one doubts its supreme importance as a contributory cause of inevitable death.

If we study the patient then, system by system, we can say that certain systems are not materially concerned, for example, the osseous system.

At first sight the clinical evidence of significant involvement of the central nervous system is not apparent. The peripheral nervous system appears indeed to be not involved. There is no paralysis and the reflexes are not abolished. The vibration sense would seem to remain. The mind may perhaps become clouded, but usually only in the last few days or hours. It is not right to say that the central nervous system is not involved at all. The picture presented is one of a general depression of its function such as might be caused by an interference with its general metabolic activity.

With regard to the general musculature, signs of weakness in malignancy have been commented upon in a recent paper by Spachman and Daniel (1953) who found that loss of vigour as a symptom was complained of in 14 of 35 patients suffering from malignant growth of the kidney. This constitutional sign was not related to anæmia. Although it was of bad prognostic significance, nevertheless, 3 of their patients survived more than two years after operation.

Loss of appetite is one of the outstanding symptoms of malignant cachexia. Appetite is said to be due to increased gastric tone together with a lowered blood sugar. There is no well-recognized evidence of interference with the sugar metabolism, and the blood sugar did not appear to be materially abnormal in the cases I have studied. Perhaps in a few, there has been a slight delay in the return of the blood sugar to the fasting level after the ingestion of glucose. There is no ready way of estimating gastric tone. The secretion of hydrochloric acid by the stomach from my observations is not abolished or depressed to a marked degree unless of course the stomach itself is the site of a growth. Attempts to improve the appetite by ordinary therapeutic measures are virtually useless. Such drugs as hydrochloric acid, pepsin and so forth, are almost valueless. On purely empirical grounds and because of its unexplained beneficial action on the appetite in tubercle, I have tried Isoniazid on 3 patients without material improvement. It would seem likely that the failure of appetite is bound up with a general failure of tone of the muscles of the alimentary canal. Certainly, there is no real similarity to anorexia nervosa or to organic disease of the pituitary.

Bound up with the failure of appetite is the loss of weight. I think we can deny the suggestion that death results from starvation. The patient is rarely sufficiently wasted at post-mortem to make this acceptable as the cause of death. In particular, his fat depots are often not emptied. In starvation. it has been shown that the basal metabolic rate is very low. In a small series of cases of malignant cachexia which I have investigated the B.M.R. has in fact been somewhat raised, in the region of + 16 to + 20%. Moreover, in certain conditions, the patient is compelled to accept into his stomach an adequate diet, as, for example, when he has a gastrostomy. The essential need of supplying to such patients a properly balanced diet of at least 2,000 calories was pointed out many years ago and is surely well recognized. Yet patients with an adequate gastrostomy presumably given a sufficient diet, do not survive malignant obstruction of the œsophagus.

Loss of weight as a symptom in renal cancer has been specially studied by Griffiths and Thackeray (1949) who found that in 16 patients complaining of loss of weight before operation, although the symptom had a bad prognostic significance, yet one was still living after six years and 5 survived more than one year after operation. I have looked into this sign and of 100 cases of renal cancer in the records of the United Birmingham Hospitals operated on more than three years ago, I have found that 26 are still alive. Of these 26 living patients 7 complained of some loss of weight before operation.

There is no evidence whatsoever that failure of renal function is a cause of death in malignant disease unless it so happens that it is associated with obstruction of both ureters. The patient may be very ill indeed with wasting and weakness, and still have a normal blood urea and no obvious sign of renal failure.

The hæmatopoietic system is almost constantly depressed, and in the absence of blood loss and sepsis, blood counts in the region of 3 million red blood corpuscles are very common. This, however, is not a fatal degree of anæmia. Life, in the absence of malignancy, can continue for months and years with such a count, and the red cell count rarely falls below some such level. It is interesting to note that in the so-called "marble-bone" disease of Albers-Schönberg, there may be encroachment on the bone-marrow space with the production of anæmia. This disease is extremely chronic. It does not seem possible to raise the blood count by any of the ordinary means at our disposal. In this respect the anæmia bears some general resemblance to that of chronic uræmia. I suspect this is a hint of some importance, to which I will refer later on.

The endocrine glands, unless as is rarely the case, directly involved, do not show well-marked evidence of gross depression of function. The blood electrolytes are not dangerously disturbed.

The patient, though weak and depressed, has none of the usually accepted clinical signs of heart failure. In the absence of a pleural effusion, he sleeps comfortably with one pillow. His heart-rate, though perhaps increased, remains regular, and if not involved by secondary growth the liver is not swollen, and frequently there is no œdema of the legs nor albuminuria. Yet death in the end is almost certainly due to arrest of the heart beat.

## Discussion

The clinical picture built up in the mind, in this disorder, is of one existing in its own right, an undoubted general constitutional effect produced throughout the body by the presence of a local malignant growth. As a clinician I have no difficulty in accepting the systems of the body as delicate sounding boards or reactors to pathological processes, and I think that perhaps it is possible to suspect what may be behind these reactions. Before developing this matter a little, I would like to discuss some of the experimental evidence and some of the modern views on cellular activity. The terminology and the techniques are somewhat unfamiliar grounds for us as urologists, but it is not impossible to follow the general gist of the lines of investigation and to appreciate what is likely to result from further exploration along these lines.

In the past, the internal chemical changes in the cell seemed so minute as to be incapable of adequate study, but by the development of many exquisite techniques and by remarkable insight, we are gradually getting in a position to make important generalizations.

Sir Rudolph Peters (1953) has stated "The wider recognition of the unique importance of intracellular enzymes in catalysing specific metabolic paths is of only recent growth and the understanding of their influence on medicine a contemporary study, the pace of which is being forced by the bridges forming between enzyme biochemistry and functional studies, in the broadest sense . . . "

It is of great interest, though perhaps not germane to the matter under discussion, to realize how conservative Nature is in the use of enzyme systems. For example, as Pryde (1931) has pointed out, the elaborate complex series of chemical changes which take place when yeast splits starch to form alcohol, have a very considerable general resemblance to the chain of reactions which occur when glycogen is split during muscular activity. And again, it is of absorbing interest to observe Nature's apparently experimental efforts in the production of oxidation in living tissues by combinations of a metal (iron or manganese or copper) with pyrrol rings, combinations—experiments, if you like, to equal her extraordinary experiments in animal external formation. It has been suggested, but unfortunately I cannot find or confirm the reference, that in the living cell there are, in fact, seven or eight basic enzyme systems.

According to Greenstein (1947, p. 318), the most striking constitutional effect in animals produced by malignant tumours appears to be in the liver. In rats, for example, carrying a wide variety of subcutaneously implanted tumours, the level of activity of one of the hepatic enzymes associated with oxidation called catalase and also the level of activity of arginase may be, and indeed usually are, considerably below the normal value. Removal of the growth will lead to a return to normal of the enzymic pattern of the hepatic tissue. This effect is not produced by, for example, pregnancy. The outstanding change in malignancy is the great depression of catalase activity chiefly in the liver but also to a lesser degree in the kidney, but there is some diminution in the activity of certain other enzymes in the liver, e.g. lipase and d-amino oxidase (Greenstein, 1947, p. 361). Greenfield and Price (1953) have isolated a fraction from experimental tumours which on injection reduces the liver catalase to approximately half of the control value in twenty-four hours. Greenstein (1947, p. 202) postulates that the marked effect of a distant tumour in lowering the liver catalase and the blood hæmoglobin of the host, would appear to suggest that there is some factor which is antagonistic to the synthesis of the iron porphyrins.

Nearly all rapidly growing tumours in mice and rats produce identical systemic effects in the host animal as shown by the marked reduction of the liver catalase activity, though even in a liver which has lost about half of its catalase activity, no microscopical changes are evident. In this respect at least, the value of the more subtle chemical techniques in recognizing such changes is apparent. It may not be so fantastic to suggest that we will soon be sending pathological specimens to the cellular enzyme chemist rather than to the histo-pathologist for report.

There seems to be considerable experimental evidence to support the theory that when a malignant growth develops in the body, it may have widespread constitutional effects, and that these effects begin to be recognizable by chemical study and that they are possibly on those enzyme systems which influence cellular oxidation or the release of energy within the cell.

Such a conception as this would seem to fit in well with the clinical picture of a widespread depression of almost every system in the body, the brunt falling perhaps on the musculature so that finally a critical degree of heart failure is reached and the heart beat stops. The experimental evidence quoted by Greenstein (1947) seems overwhelming and incontrovertible that local cancer can cause a general constitutional effect, and surely clinical experience, if properly assessed, is also unequivocal on this point.

I, for the moment, am more attracted to the view that the malignant growth excretes something into the circulation which damages the body rather than that it abstracts such a substance. I have found that transfusing a patient with blood (½ pint at fortnightly intervals) appeared to make no difference to the steady downward path, nor has the administration of all the known vitamins in large quantities seemed to have any significant effect. Girdwood (1953) has recently pointed out that folic acid when injected into patients in 5 mg. doses is not excreted in the usual quantity in the urine in the presence of advanced malignant disease, and he seems to favour the explanation that the tumour tissue competes with the host for folic acid or its derivatives. It so happens that I had treated a patient dying from cancer of the prostate with folic acid some months ago. I had not noticed any very certain benefit in his general condition. A single case means very little, of course, and the folic acid might very possibly have benefited the neoplasm rather than the patient.

Cruickshank (1953), working in Professor J. R. Squire's Department in the University of Birmingham, making use of tissue culture as an indicator has found that serum from a patient suffering from malignant cachexia neither inhibited the growth of the epidermis when compared with a control nor did it inhibit the rate of oxygen consumption of the cultured tissue under the same conditions. These were pilot experiments and perhaps need confirmation. It is now proposed to note whether the medium bathing a tissue culture of malignant cells becomes toxic to a culture of normal cells. If so, I think we will have something tangible to work upon. The fact that a growth of skin in culture was not inhibited by serum from a cachectic patient is not necessarily significant. If we consider that the main functions of a cell are to multiply, to differentiate and grow, to secrete and perhaps merely to live, it is quite easy to accept that only some of these functions may be depressed under certain conditions. In the patient suffering from advanced malignant disease, those tissues which ordinarily continue to multiply and differentiate in the body, are not very greatly inhibited, the leucocytes continue to be formed apparently normally, and an operation wound will heal fairly well. Although perhaps secretory activity is depressed, the outstanding impression beyond a doubt is of diminution of energy production behind every process in the body. This seems to me a valid clinical observation and one which justifies us to encourage the enzyme chemist to narrow his study down to the chain of reactions which lead to energy release. The other hint would seem to be the intractable anæmia. The suggestion of Greenstein (1947, p. 202) that there is a defect in the metabolism in the iron porphyrins may serve as a link between these two pointers and I think they open up a vista of lines of enquiry which are quite promising and which are engaging our attention.

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The following cases and specimens were shown:

**An Unusual Pyelogram.**—Mr. J. G. YATES BELL.

**Polycystic Disease of the Kidneys and Liver.**—Mr. JOHN PRICE for Mr. J. G. YATES BELL.

**Localized Polycystic Disease of the Kidney.**—Mr. JOHN SWINNEY.

**Kidney with a Simple Cyst and Carcinoma.**—Mr. G. C. TRESIDDER.

**Disappearance of Chest Shadows after Removal of Hypernephroma.**—Mr. M. T. PHEILS.

**Hypernephroma with Metastases Successfully Removed from Lung and Brain.**—Mr. A. R. C. HIGHAM.

**Spontaneous Rupture of Hypernephroma with Retroperitoneal Hæmatoma.**—Mr. HOWARD G. HANLEY.

**Spontaneous Adrenal Apoplexy.**—Mr. H. K. VERNON.

**Two Parathyroid Tumours.**—Mr. J. H. TASKER for Mr. J. C. ANDERSON.

**Vesical Diverticulum with Carcinoma in Female.**—Mr. H. K. VERNON.

**Anomaly of Bladder.**—Mr. B. H. PAGE.

**Carcinoma of Ureter.**—Mr. ALEX. E. ROCHE.

(1) **Reconstruction of the Complete Penis Following Amputation for Carcinoma** (by Mr. Geoffrey Parker), **Using the Gillies Double Tube Pedicle Technique.** (2) **Reconstruction of the Penis after Ectopia Vesicæ with Prolongation of Ejaculatory Ducts to Glans (after Transplant of Ureters into the Colon in Infancy by Sir Lancelot Barrington-Ward).**—Mr. PATRICK CLARKSON.