LATENT CARCINOMA

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by

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I WANT TO discuss to-day a concept of tumour growth which is by no means new but it is one which many people find difficult to accept completely. Much of what I have to say I consider to be proven fact but much is speculation and I shall try to indicate clearly into which group my statements should be placed. It is possible that you may not agree with some of the conclusions which I have drawn and some of them you may consider to be based on insufficient evidence. If this be so I can only defend myself by reminding you that Emmerson once said, "I can receive instruction from no man, but only provocation." My purpose in this lecture is to provoke—to suggest to you a possible explanation for a number of unexpected findings.

In Fig. 1 I have shown three different patterns of tumour growth. The first type is the rapidly growing tumour which soon kills the patient—

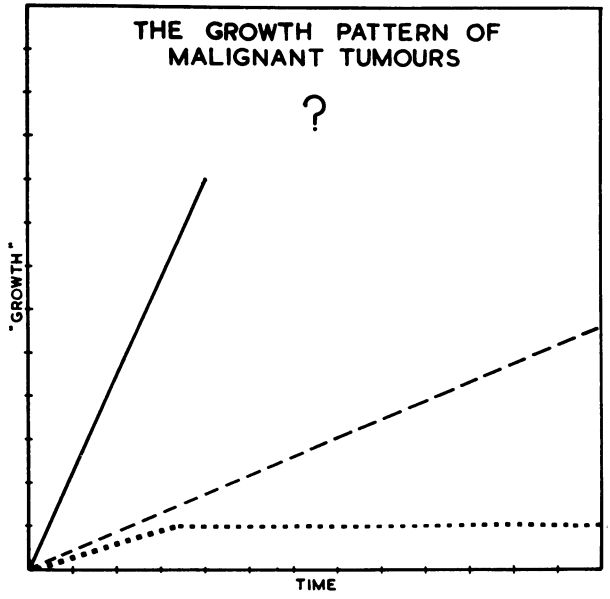

Fig. 1.

perhaps within the first year; the second is the slow growing tumour which may be present for many years and may not even be an immediate

cause of death. These two groups are well recognised. The third group is the group I propose to discuss—the latent carcinomas. The growth pattern which I suggest for this type of tumour is of the plateau type. The tumour reaches a certain stage in its development, which then ceases, and the tumour remains latent at this level, for a considerable period. In this lecture I hope to present to you the evidence which suggests that certain tumours may behave in this way.

Latent carcinoma of the prostate

When I began my work on the prostate I was aware—but rather vaguely—that a number of people had published papers which purported to show that if the prostate glands of elderly men were examined microscopically a number of them would be found to contain histological cancers—about 10 per cent. or more. There is a strong emotional barrier against believing the unexpected and like many other pathologists and clinicians I did not choose to accept these figures. However when I took the trouble to read these papers I found that since 1935 no fewer than nine had been published and I have summarised the findings from eight of these in Table I. The ninth paper I have not been able to obtain.

LATENT PROSTATIC CANCER			
SERIES	NO. OF CASES	NO. WITH CANCER	% WITH CANCER
1935	292	41	* 14%
1935	229	46	20·5 %
1937	100	30	30 %
1938	940	185	21 %
1941 (A)	364	54	* 14·8 %
1941 (B)	50	22	44 %
1944	210	54	25 %
1949	99	16	16 %
1953	254	41	15 %
1954	178	69	37 %

Table I.

The first is by Professor Rich who examined only one section from each case. He found 41 carcinomas in 292 autopsies (14 per cent.) and felt that a more thorough investigation would have shown more. Another pathologist, Kahler (1939) thought that the number of tumours found

was directly related to the number of sections examined. Baron and Angrist (1941) described two series which illustrate this point. In the first, 364 cases were studied by one or occasionally more, random sections from the prostate and 54 of these were found to have malignant foci (14.8 per cent.). When a second series of 50 prostates were more carefully examined by " step sections " through the gland 22 (44 per cent.) were found to contain carcinomas. On the face of it this seems a fantastic figure and one felt that the only possible explanation was that the criteria of malignancy which were used were not valid.

I therefore began to collect a number of specimens myself and examine them critically. The pelvic viscera, i.e., bladder, prostate and rectum, were removed in one piece from 220 males. In all cases death had been sudden or unexpected and an autopsy had been required by the Coroner. One case had a clinically diagnosed carcinoma of prostate and this case was excluded from the series. Otherwise there was no selection of cases but the series obviously contains a large number of elderly men. Heart disease, especially coronary insufficiency was the commonest cause of death. The tissues were fixed whole, cut into slices about 4 mm. thick and large histological sections were then made from these slices. By this method the whole of the prostate and its surrounding tissues could be examined and the site and extent of any changes easily noted.

When these sections were examined using the ordinary criteria of malignancy of the diagnostic morbid histologist I too found that carcinomatous areas were very common. In fact my figures were rather higher than some previously reported. There were 69 carcinomas in the 220 cases, i.e., about 30 per cent. or 37 per cent. in men over 50 years of age. By this time I began to wonder whether the fault lay in me so I took the sections to Dr. Cuthbert Dukes at St. Peter's Hospital where a large number of prostatic specimens are examined. He agreed that most, if not all, were histologically malignant. I then took a representative selection of these slides to about a dozen different experienced pathologists with similar results. The apparent discrepancy between this high incidence of prostatic cancer in autopsy material when compared with the low incidence (2-5 per cent.) in prostates removed surgically for benign enlargement is explained by the fact that prostatic cancer almost invariably begins in the outer zone of the prostate which is not removed in the usual operations of prostatectomy.

There is no doubt that these lesions in the prostate have the morphological characters of malignant tumours and their structure and age incidence is identical with that seen in typical metastasising prostatic cancer. I have described the structure of these tumours in detail elsewhere (Franks, 1954). All showed cellular and structural dedifferentiation and many showed infiltration of the capsule, lymphatics and blood vessels which must, I think, be taken as presumptive evidence of malignancy. In one case secondary deposits were found in two internal iliac lymph

nodes, but an extensive search for distant metastases was not possible. These tumours therefore have the structural and some biological characteristics (particularly infiltration) of cancer but apparently lack the power of rapid growth. This is not directly related to size because, although many were small, others had almost entirely replaced the prostate. To say that they look like tumours but are not is to beg the question. *Essentia non sunt multiplicanda praeter necessitatem.* However the fact remains that none had apparently caused the patients any harm and were certainly not related to the immediate cause of death.

Age incidence of prostatic cancer

Before discussing the significance of these findings I want to describe the age incidence of prostatic cancer. It is found more frequently with increasing age in clinical and autopsy cases, both in those dying of the disease and those in which it is an incidental finding. The greatest incidence is in the seventh and eighth decades and most deaths occur in the eighth (Figs. 2-4). The figures for my series of " incidental " cases

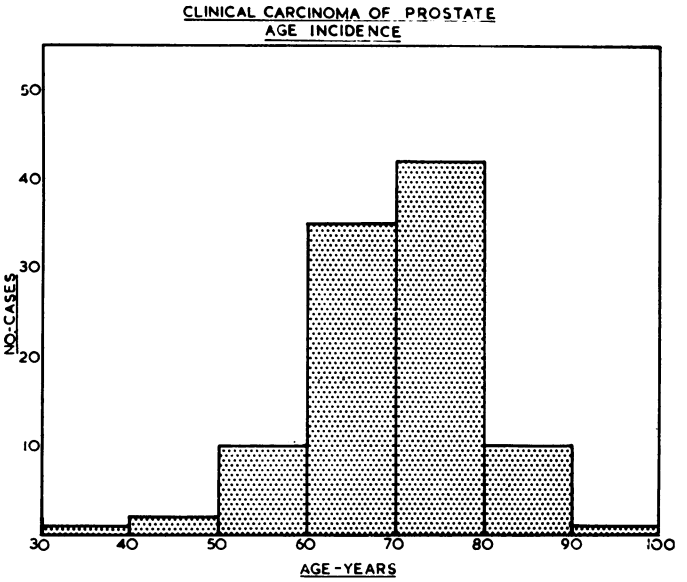

Fig. 2.

follow a similar pattern. In the sixth and seventh decades about a third of all cases have these tumours, in the eighth decade nearly a half, in the ninth more than three quarters and in the tenth all cases. In fact the suggestion is that, given time, it would be an invariable finding.

What is the significance of these findings ? These are apparently true cancers but they seem to do no harm and we can therefore correctly

call them latent cancers. That is to say they exist but do not develop or become manifest. Latency, so defined, is not directly related to tumour size, or to cellular differentiation. While it is true to say that many of these tumours were small and made up of relatively well differentiated cells others were large and anaplastic areas were found in almost one-fifth of the cases. Many, as we have seen, had invaded capsule, blood vessels and lymphatics and I think it possible that distant metastases may have occurred. The common factor in all cases was the absence of the local or general effects normally produced by clinically malignant tumours. There were apparently no local symptoms and if there were distant

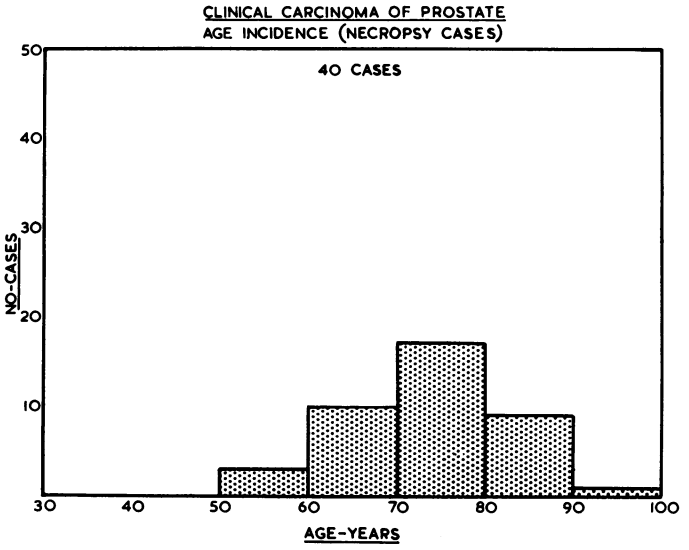

Fig. 3.

metastases these too did not reveal themselves. Now it seemed to me remarkable that this state of affairs should occur in the prostate alone, and I then began to realise that the same thing happened in other organs.

Latent carcinoma of lung

In the lung Raeburn and Spencer (1953) have recently described the results of a very painstaking study. The whole of both lungs removed from adults at autopsy was carefully examined and all suspicious nodules were studied histologically. By this means 13 small carcinomas and two larger ones were found in a comparatively short time. Four of the tumours, beginning in the main lobar bronchi, were found to start as intra-epithelial carcinomata. The remaining 11 were all found in association with scars near the periphery of the lungs. Seven of these were frank carcinomas and four showed features resembling the carcinoid type of bronchial

adenoma but were provisionally regarded as probable oat cell carcinomata. As with the prostatic tumours lymphatic permeation was found and in one case there was a metastasis in a rib.

Latent carcinoma of kidney

Small tumours—the so-called adenomas—are common in the kidney and have been fully described by Nicholson (1923), Newcomb (1936), Trinkle (1936) and Willis (1953). I can do no better, I think, than summarise what Willis has to say about these tumours. Cortical adenomas are well defined but often not encapsulated. They vary in size from just

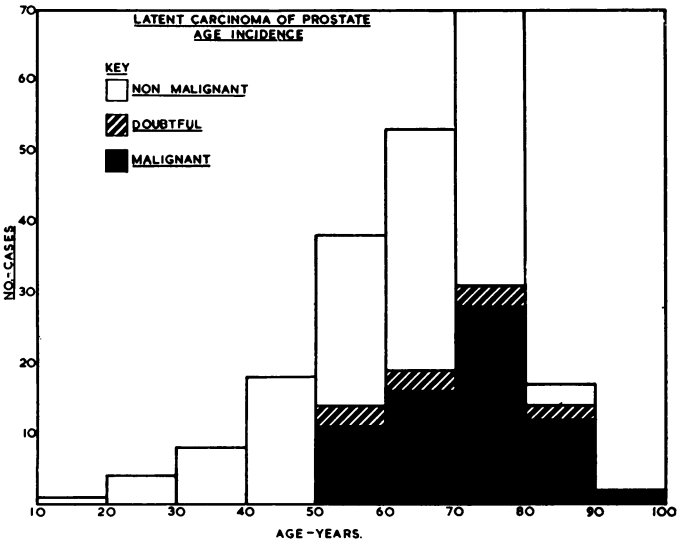

Fig. 4.

visible dimensions up to 2 cm. or more in diameter and are frequently multiple. They are found chiefly in middle-aged or old people and are uncommon in youth. The structure varies. Many of the tumours have an intra-cystic papillary structure while others are tubular or solid. In some the epithelium consists mainly of small cubical cells but in others the cells are larger and foamy and closely resemble those of clear cell renel carcinomas. Many show no encapsulation. Others may have thick fibrous capsules but these are rarely complete and extension of the growth through the capsule is usual. It is difficult to say whether these tumours are neoplastic from the beginning or arise as focal areas of hyperplasia which later become neoplastic. Are adenomas related to carcinomas? "Anyone," says Willis, "who has examined and compared the structure of these tumours will have no hesitation in joining Newcomb and Trinkle in a strongly affirmative answer. Indeed a sharp separation of adenomas and carcinomas is not possible. Some adenomas show a structure

indistinguishable from that of carcinomas, and it is purely a matter of opinion whether we regard such tumours as atypical adenomas or as young carcinomas which we happened to have discovered before they have metastasised. Many an ' adenoma ' found incidentally at necropsy differs not one whit from some of those small symptomless carcinomas which have produced precocious metastases. Renal tumours, like other tumours, differ in their individual rates of growth, invasiveness and metastasising proclivities. It is proper," he goes on, " that those tumours which for long periods grow slowly, attain a uniform highly differentiated structure and fail to spread, should be called ' adenomas ' to distinguish them from their more active fellows." However I suggest that they might more properly be called latent carcinomas.

Latent carcinoma in other organs

Few other organs have been as thoroughly examined as the prostate, lung and kidney. Consequently the figures which I give relating to other organs can represent only the results of a relatively incomplete investigation, nevertheless I hope to show you that even the most casual search will show that small latent carcinomas occur in other organs also.

It is well known that carcinoma of the *thyroid* gland may remain latent and reveal itself only by the development of distant metastases in bone, lung or liver (Willis, 1953 ; Mitchell, 1945). Many of these tumours are so well differentiated that they can be distinguished only with difficulty —if at all, from normal thyroid tissue—hence the so-called benign metastasising goitre.

Unsuspected carcinomas in surgically removed goitres often invading blood vessels, have been reported in many cases : from 1-5 per cent. in the United States and up to 10 per cent. in Switzerland. The incidence at autopsy varies from 0·1-0·4 per cent. in the U.S.A. to 1 per cent. in Switzerland (Anderson, 1953). It is more than probable that these figures are much too low as we shall see if we examine a large series more carefully. Schlesinger and his colleagues (1938) reported on a series of 1,373 autopsies with six carcinomas (0·4 per cent.). However these figures were collected from autopsy reports from three different hospitals and a histological section or sections were available in only 74 cases. The six carcinomas were found in these 74 cases, giving an incidence of 8·1 per cent. Obviously sections of the whole thyroid in all cases would probably have shown a larger number of carcinomas.

The *adrenal* gland is another endocrine gland where small cortical nodules are commonly found. Again I shall quote Willis. " No sharp separation of benign and malignant growths is possible. . . . Many of the tumours have a well differentiated structure closely resembling that of the adrenal cortex. When such tumours are well circumscribed and devoid of metastases and have not recurred after surgical removal no objection can be raised to calling them adenomas. But tumours of similar structure may recur or metastasise."

In the *gastro-intestinal tract* too, these latent carcinomas can also be found. Obviously the finding of a small, often microscopic, lesion in the 30 feet (9 metres) of the alimentary canal must depend largely on chance and the fact that I can show you four seems to me to be of some significance. The first is from a lady of 60 years, who had hypertension and rheumatoid arthritis and died from a severe attack of bronchopneumonia. At autopsy she also had a small flat plaque about $0{\cdot}8 \times 0{\cdot}5 \times 0{\cdot}5$ cm. in the mucosa of her transverse colon. Histologically this was a typical adenocarcinoma. The remaining cases arose in the stomach. The first is from a man of 51 years who had a duodenal ulcer for many years. He was treated by partial gastrectomy. In the operation specimen there was a shallow depression near the pylorus which looked rather like an ulcer scar. The whole lesion measured about $0{\cdot}8 \times 0{\cdot}3 \times 0{\cdot}4$ cm. Histologically this was a cuboidal cell tubular and solid trabecular carcinoma of stomach. The second case was described by Dr. Mayne (1953). This man, 37 years of age, had tabes dorsalis with gastric crises which did not respond to antisyphylitic treatment. At a second laparotomy a diffuse area of thickening in the stomach wall was found and removed by partial gastrectomy. The abdominal crises continued and he was finally treated by unilateral chordotomy. Histology of the lesion in the stomach showed a very small well differentiated adenocarcinoma.

The third case was shown to me by Dr. Helyer, and is to be described by him more fully. This is a most instructive case. A man of 59 years complained of severe pain in the back and legs since August, 1953. X-ray examination showed destructive lesions in ribs, spine and pelvis and a biopsy suggested that these were metastatic deposits from an occult renal carcinoma. At autopsy early in September, 1953, a small histologically typical renal carcinoma was found in the right kidney. In the stomach however there was a button-like nodule about 2·5 cm. in diameter covered by intact mucosa. Histological examination showed this to be a typical solid trabecular carcinoma of stomach with secondary deposits in a regional lymph node. Sections from the prostate showed a nodule of dark cell small acinar prostatic carcinoma.

In the *liver*, too, small adenomas and areas of hyperplasia in cirrhotic livers are commonly seen. No sharp line of distinction can be drawn between hyperplasia and benign and malignant neoplasia and it is known that malignant disease in the liver frequently begins in an organ which is already fibrotic. I have not been able to find any figures on the incidence of these unsuspected liver tumours.

Latency in *chorioncarcinoma* has also been described. Brown and his colleagues (1940) reviewed the literature and accepted three cases. : 1. Uterine chorioncarcinoma three years after bilateral oophorectomy and five and a half years after the original mole (Kröning) ; 2. Three years after hysterectomy (Cary) ; 3. Uterine chorioncarcinoma at the age of 70, i.e., 15 years after the menopause and presumable cessation of ovulation (Dorr and Cutler). They also describe a fourth case of their own. In

this case a large chorioncarcinoma was found in the lung nine years after a hydatidiform mole. The uterus was removed seven years before. No sign of malignancy was found in the uterus or the mole. In all these cases it is possible to argue that the original mole was already malignant but the fact of latency remains.

Carcinoma in situ in skin, i.e., Bowen's disease, and in the cervix are both well recognised conditions which may fall into the category of latent carcinoma. Both have the cytological criteria of malignancy but may remain latent for many years before developing into active carcinomas.

The *melanomas* form another group of tumours in which this phenomenon of latency can also be seen. Malignant melanoma is hardly ever seen in children yet there is a well recognised group of these tumours—the so-called juvenile melanomas—which are histologically identical with those seen in adults but do not metastasise (Allen, 1953). Latency in secondary deposits of malignant melanoma and other tumours is of course well known. This subject was discussed by Professor Hadfield in his Kettle Memorial Lecture (1954). It is worth noting here that a primary tumour may have become manifest but metastatic deposits may remain latent for many years. There is thus a dissociation between primary and secondary tumours. Changes need not necessarily affect both simultaneously.

So far I have discussed only human tumours and I think I have shown that there can be no question about the existence of latent carcinoma. They are found most frequently in organs which are small and easily examined, e.g., prostate and kidney, but it is possible that they are equally common in other organs. Many may have already spread locally or by lymphatics and blood vessels.

Certain *experimental tumours in animals* behave in a similar fashion and I will give two examples of this. Gardner (1945) described two testicular interstitial cell tumours which arose in mice but which failed to grow when transplanted into 34 genetically susceptible mice. Seventeen of these were killed at intervals from 51 to 204 days. After this time 17 survivors were treated with oestrogens and in 16 animals the grafts began to grow and after a while some continued to grow even when no further treatment was given. The transplanted tumour fragments therefore remained latent until the environment was suitable. Many of the untreated grafts were very small and definite tumour cells could not be detected histologically.

Foulds in an earlier Imperial Cancer Research Fund Lecture in this College (1951) described a series of mammary carcinomas in mice which grew during pregnancy and regressed after littering, to remain latent until a subsequent pregnancy.

Latency and progression in tumours

The work of Berenblum (Berenblum, 1941 ; Berenblum and Shubik 1947) and Rous (quoted by Foulds) has thrown some light on this problem. Two phases in tumour growth have been recognised ; a phase of initiation in which a small proportion of cells are permanently altered and a phase of development or promotion during which the cells multiply and produce visible and finally malignant tumours. The phase of initiation in skin tumours requires a specific carcinogen but the phase of development may be brought about either by a carcinogen or by a non-specific irritant which would not by itself normally produce a tumour. The initial application of the carcinogenic stimulus may cause no visible changes in the affected cells or it may cause a lesion which is histologically malignant but disappears if the stimulus is withdrawn. The development of new and irreversible properties from initiation to malignant neoplasia, Foulds has called " progression." In the experimental animal progression may halt spontaneously for a long time at any point and may not necessarily reach an end-point within the lifetime of the host. More recently Berenblum and others have suggested that after initiation the promoting stimulus leads to local proliferation, but until the colony reaches a so-called " critical size " it is not " self-perpetuating." Once it reaches this critical size it then provides its own stimulus to growth and develops as a true neoplasm. There are thus four stages :

(1) Initiation
(2) Promotion
(3) Critical size
(4) Clinical tumour.

The period between stages three and four can conveniently be called the stage of " pre-clinical tumour."

The latent carcinomas could therefore form a mixed group which included all tumours from the stage of initiation to that of the " pre-clinical " tumour and the behaviour of each individual tumour would depend on its stage. Similarly many of the problems of delayed and latent metastases could be explained if one assumed that *metastasis is not a property of fully developed tumours only but can occur at any stage in progression.* The development of the metastatic tumour also would depend on the stage of development of the metastatic cells. It seems to me not improbable that this should occur because we have seen that vascular and lymphatic involvement are common in many of the latent carcinomas and it is well known that even apparently normal tissues may be found as emboli in distant organs.

The causes of latency

In the experimental animal, some of the causes of latency can be recognised. The transplanted testicular tumours remained latent because oestrogen was required for their growth. Skin tumours did not appear or

regressed because a specific or non-specific irritant was not applied or was applied for too short a time. The breast tumours in Foulds' mice regressed when a stimulus derived from the pregnant animal disappeared. I have made the assumption here that regression and progression represent opposite phases of the same process. If the factors responsible for progression are removed the tumour regresses and may remain latent. That is to say these tumours are dependent on some factor or factors for their continued growth. These factors are many and varied. Another group of workers (Moon *et al.* 1952) have shown that removal of the pituitary will prevent the appearance of spontaneous or induced tumours in rats. Tumours of the ovary and thyroid which were dependent on the presence of the pituitary have also been described. This work has been summarized recently by Furth (1953). Others have shown that restriction of diet will also prevent or delay the appearance of tumours in animals (see Burrows and Horning, 1952, for references). Regression following the development of an immunity reaction to certain transplanted tumours in animals has also been reported but specific antibodies to spontaneous neoplasms have never been convincingly demonstrated. This subject has been exhaustively reviewed by Hauschka (1952). We also know that cell growth may be retarded in vitro by physical means, particularly freezing, but obviously in vivo the mechanism concerned must be much less crude.

In man the causes of latency are even more obscure. We do not know whether it is due to factors in the host or in the tumour or whether it is due to the interaction of both. Greene (1952, for summary) has described the development of a state which he calls autonomy, in malignant tumours. He maintains that the change from a benign to a malignant process is progressive and that when the tumour is fully malignant it is capable of independent growth even when transferred into an animal of another species. Latent tumours by this definition have not become autonomous. However this is only another way of describing a given set of facts, and to describe is not to explain.

Of the factors known to cause latency or regression in the experimental animal only certain hormones have been shown to have a similar though temporary effect in man. Huggins (1941) showed that the growth of prostatic cancer could be retarded in some cases by limiting the secretion of androgen either by castration or treatment with oestrogen. This growth retardation may last for many years in some cases (Fergusson and Franks, 1953). Some cases of breast cancer may respond in the same way after treatment with oestrogen or androgen. More recently Huggins (Huggins and Bergenstal, 1952) has shown that regression in mammary and prostatic cancer may follow removal of both adrenals and the removal of the pituitary may have a similar effect. It is possible therefore that latency in prostatic cancer may be due to the hormonal environment but there is no absolute proof of this. The causes of latency in other organs is unknown.

Discussion

I have so far confined myself to a discussion of relatively well-established facts. I now propose, if you will allow me, to speculate. The existence of latent carcinoma has been established with certainty only in the prostate, kidney, lung and perhaps the thyroid and stomach. In other organs the examples I have given may perhaps have been only chance findings and one cannot necessarily assume that changes which take place in one organ also take place in another. However, the conclusions which I shall draw are tentative and represent only one possible explanation of many which may be drawn from the same given facts. It represents only a basis for discussion.

The conclusions which I have drawn are these. There is a progression, in Foulds' sense, in human as well as in animal tumours. Latent tumours are at a stage in their progression at which they are incapable of rapid and sustained growth. They may, however, have the power to infiltrate and perhaps form metastatic deposits which also remain latent. Latency is not directly related to histological differentiation or to the size of a tumour. It may be dissociated : that is to say it may affect either primary or secondary tumours or it may affect both simultaneously. There is no reliable method of distinguishing between latent and active carcinomas although Greene believes that the ability of a tumour to grow after transplantation into an animal of another species (heterotransplantation) may be an indicator of its biological activity. There are no morphological differences between the two groups. The cause of latency is not known but it may be due to local factors in the tumour or general factors in the host. In some cases these general factors may be hormones. To return for a moment to latent tumours in man we have seen that these tumours are most commonly found in the prostate, kidney, lung, thyroid and stomach. Apart from the fact that these organs are small and easily examined they share one other characteristic—in all the results of radical surgery as a cure for cancer are disappointing particularly when compared with the results obtained in other organs, e.g., the rectum, where latent carcinomas are apparently not seen. Is this relationship coincidental ? Is it due to differences in the " growth habit " or accessability of tumours in different organs or is it due to the fact that in certain organs, where these latent carcinomas are common, the tumour may have already spread before it becomes manifest ?

If this is so investigation of the factors responsible for latency in tumours should be a rational field of research. Obviously even the most rapidly growing metastatic tumours cannot be truly autonomous. They must be dependent on factors which we are at present unable to recognise and deprivation of these factors may lead to regression and latency. One is encouraged to think that this is so by the fact that regression may occur unexpectedly in the most malignant of tumours, as for example the case reported by Sumner (1953). This patient was a woman of 30 who had a malignant melanoma, with secondary deposits

in the skin, breast and inguinal lymph nodes. Some of the larger tumours were incompletely removed as a palliative measure. Histologically the tumours had the structure of a typical malignant melanoma. Seven and a half years after the original tumour was first seen she was alive and well but all areas on the skin which had borne melanotic tumours were depigmented. Here then is a case in which a rapidly growing malignant tumour suddenly regressed and apparently disappeared. Other similar cases, with tumours in other organs have been reported but this will serve as a convincing example.

There remain a number of other questions. Do latent carcinomas develop into actively growing clinical cancers? Do all cancers begin in this way ? Should our diagram of possible patterns of tumour growth be amended as in Fig. 5 which suggests that any given tumour may follow

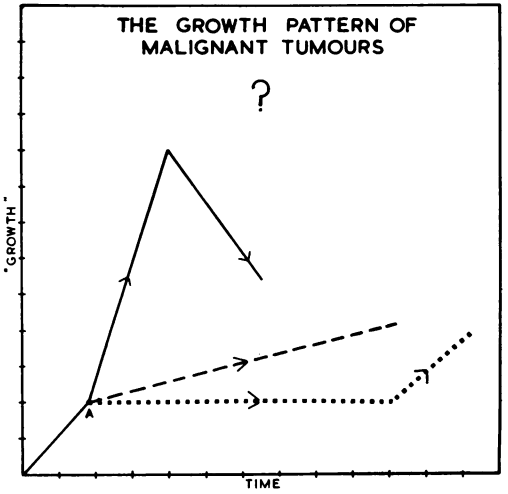

Fig. 5.

one of three possible paths—that of rapid growth, slow growth or latency ? I use " growth " here in the sense of biological development or progression rather than increase in size. The change which I have shown as taking place at point A could obviously occur at any level and at any stage regression might be possible. Do all tumours follow this pattern or does each begin with its own inherent pattern of growth? Do tumours in different organs begin in different ways—some as latent carcinomas and others as active carcinomas *ab initio*? Has this possible difference in origin any relationship to the results of surgical treatment? To these questions I have no answers.

SUMMARY

If certain organs, particularly the prostate, lung, kidney, thyroid and perhaps stomach, are carefully examined, large or small carcinomas can be found in them with remarkable frequency. One can reasonably expect

to find an occasional small tumour by chance in any organ but the fact that these tumours are found in such a high proportion of cases must mean that their development is retarded. The tumours are latent tumours. Why they remain latent we do not know and we can only speculate on their significance. The answers to these problems seem to me to be of some importance.

My thanks are due to Dr. C. E. Dukes and Dr. J. Stretton Young for much helpful and constructive criticism. Figs. 2, 3 and 4 are reproduced from the *Journal of Pathology*, and I am indebted to Mr. J. D. Fergusson for the information on which Fig. 2 is based.

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PROFESSOR FREDERIC WOOD JONES, D.Sc., F.R.S., F.R.C.S.

The Council have learned with deep regret of the death on 29th September of Professor Frederic Wood Jones, Honorary Curator of the Hunterian Collection of Human and Comparative Anatomy. An appreciation will appear in the next issue of the *Annals*.