CANCER

Edited by

RONALD W. RAVEN
O.B.E. (Mil.), T.D., F.R.C.S.

Joint Lecturer in Surgery, Westminster Medical School, University of London; Surgeon, Westminster Hospital Teaching Group; Surgeon, The Royal Marsden Hospital; Surgeon, The French Hospital

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PART II

PATHOLOGY OF MALIGNANT TUMOURS

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CONTRIBUTORS TO THIS VOLUME

NORMAN ASHTON, M.R.C.P., M.R.C.S.
Reader in Pathology, University of London; Director, Department of Pathology, Institute of Ophthalmology, London; Consultant Pathologist, Moorfields Eye Hospital, London

J. W. CLEGG, L.R.C.P., M.R.C.S.
Pathologist, Brompton Hospital, London

A. H. CRUICKSHANK, M.D. (ABERD.), PH.D.
Senior Lecturer in Pathology, University of Liverpool; External Examiner in Pathology, National University of Ireland

GEORGE J. CUNNINGHAM, M.B.E., M.D., B.S.
Sir William Collins Professor of Pathology and Conservator of the Pathological Collection at the Royal College of Surgeons of England

EDITH K. DAWSON, M.A., M.D.
Melville Trust Research Fellow, Forrest Road Laboratory, Department of Pathology, University of Edinburgh; formerly Histologist, The Royal College of Physicians' Laboratory, Edinburgh.

CUTHBERT E. DUKES, O.B.E., M.D., M.SC., F.R.C.S.
Consulting Pathologist and Director of Research Laboratory, St. Mark's Hospital, London

L. FOULDS, M.A., M.D.
Pathologist, Chester Beatty Research Institute, Institute of Cancer Research, The Royal Cancer Hospital, London

L. M. FRANKS, M.D., B.S.
Pathologist, Clinico-Pathological Laboratories, Imperial Cancer Research Fund, London

I. FRIEDMANN, M.D., D.C.P.
Director, Department of Pathology, The Institute of Laryngology and Otology, London; Reader in Bacteriology, University of London; Honorary Consultant Pathologist, Royal National Throat, Nose and Ear Hospital, London

MAGNUS HAINES, M.D., B.S., F.R.C.O.G.
Consultant Pathologist and Director of the Pathology Department, Chelsea Hospital for Women in association with the Institute of Obstetrics and Gynaecology, University of London; formerly Erasmus Wilson Demonstrator, Royal College of Surgeons of England

PAO-CHANG HOU, M.D. (PEKING)
Professor of Pathology and Bacteriology, University of Hongkong; Pathologist to Queen Mary Hospital, Hongkong; Consulting Pathologist to the Government of Hongkong

K. INGLIS, M.D. CH.M. (SYD.), F.R.A.C.P.
Emeritus Professor of Pathology in the University of Sydney; formerly Director of the Kanematsu Memorial Institute of Pathology, Sydney Hospital, Sydney, Australia.

JAMES W. KERNOHAN, M.D., M.A., D.P.H.
Professor of Pathology, Mayo Foundation, Graduate School of University of Minnesota; Chairman, Sections of Pathologic Anatomy and Surgical Pathology, Mayo Clinic, Rochester, Minnesota

JOHN WINGRAVE LANDELLS, M.A., M.B., B.CH., M.R.C.P.
Reader in Pathology in the University of London, at the London Hospital Medical College; Assistant Pathologist to the London Hospital; Honorary Consultant Pathologist in Morbid Anatomy to the Royal Navy

BERNARD LENNOX, M.D., PH.D., M.R.C.P.
Senior Lecturer in Pathology in the University of Glasgow; Assistant Pathologist to the Western Infirmary, Glasgow; formerly Lecturer in Pathology, Postgraduate Medical School of London

DAVID A. MACFARLANE, B.SC., M.CH., F.R.C.S.
Surgical Tutor, The Medical College of St. Bartholomew's Hospital, London; Senior Surgical Registrar, The Royal Marsden Hospital, London

AGNES R. MACGREGOR, M.D. (ED.), F.R.C.P. (ED.)
Consultant Paediatric Pathologist, South-Eastern Regional Hospital Board, Scotland; Reader in Pathology of Diseases of Children. University of Edinburgh

J. L. PINNIGER, M.A., D.M., M.R.C.P.
Physician in Charge Clinical Laboratory, St. Thomas's Hospital and Medical School, London

R. C. B. PUGH, M.D.
Pathologist to St. Peter's and St. Paul's and St. Philip's Hospitals, London, and to the Institute of Urology, University of London

RONALD W. RAVEN, O.B.E. (MIL.), T.D., F.R.C.S.
Joint Lecturer in Surgery, Westminster Medical School, University of London; Surgeon, Westminster Hospital Teaching Group; Surgeon, The Royal Marsden Hospital; Surgeon, The French Hospital.

GEORGE P. SAYRE, A.B., M.D., C.M., M.S. IN PATH.
Assistant Professor of Pathology, Mayo Foundation, Graduate School of University of Minnesota; Member of Section of Pathologic Anatomy, Mayo Clinic, Rochester, Minnesota.

H. A. SISSONS, M.B., B.S.
Morbid Anatomist, Institute of Orthopaedics, Royal National Orthopaedic Hospital, London

RODNEY SMITH, M.S., F.R.C.S.
Surgeon, St. George's Hospital, London

H. SPENCER, M.D., PH.D., F.R.C.S., D.T.M. & H.
Reader in Morbid Anatomy and Histology, University of London; Honorary Consultant Pathologist, St. Thomas's Hospital, London

T. W. SUTHERLAND, M.D. (LEEDS)
Senior Lecturer in Pathology, University of Leeds

W. ST. C. SYMMERS, M.D. (BELF.), M.R.C.P.
Professor of Morbid Anatomy, Charing Cross Hospital Medical School, University of London; Honorary Consultant Pathologist, Charing Cross Hospital, London

A. C. THACKRAY, M.A., M.D.
Reader in Morbid Anatomy and Histology, University of London, at the Bland-Sutton Institute of Pathology; Consultant Pathologist, the Middlesex Hospital, London

A. D. THOMSON, M.A., M.D., M.R.C.P.
Senior Lecturer in Pathology at the Bland-Sutton Institute of Pathology, Middlesex Hospital, London; Honorary Pathologist, the Hospital of St. John and St. Elizabeth, London

R. A. WILLIS, D.SC., M.D., F.R.C.P.
Emeritus Professor of Pathology, University of Leeds

THEODORE WINSHIP, M.D.
Senior Attending Pathologist, Children's Hospital, Episcopal Eye, Ear and Throat Hospital, and Garfield Memorial Hospital, Washington, D.C.; Consultant Pathologist, The Clinical Center, National Cancer Institute, Bethesda, Maryland; The Surgeon General, U.S. Army, and Walter Reed Army Hospital, Washington, D.C.

PART II

PATHOLOGY OF MALIGNANT TUMOURS

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CONTENTS

CHAPTER 1

THE GENERAL PATHOLOGY OF MALIGNANT TUMOURS

GEORGE J. CUNNINGHAM

DEFINITION

AN IDEAL definition is both brief and accurate. In view of the large number of tumours known, together with their variations of behaviour, it is not surprising that no satisfactory general definition exists at present. Many previous definitions failed to define, and in the absence of evidence of the mechanism of origin they are confined to describing what tumours do rather than what they are. For example, Powell White's definition (quoted by Adami, 1909) was as follows: "A tumour proper is a mass of cells, tissues, or organs resembling those normally present but arranged atypically. It grows at the expense of the organism without at the same time subserving any useful function." Ewing (1919) defined a tumour as "an autonomous new-growth of tissue." Neither definition is satisfactory; Powell White's includes malformations, and Ewing's the foetus *in utero*. A more serious criticism can be made of the descriptive terms; for example, "autonomous" conveys an impression of lawlessness or anarchy, a conception only applicable to malignant tumours that grow most rapidly. In a similar way it became implied that all tumours were functionless. This idea is easily refuted when it is recalled that osteogenic sarcomas may produce bone; primary hepatic carcinoma, bile; alimentary carcinoma, mucus; and thyroid cancers, thyroxine. Willis (1948) gave a more satisfactory definition because he emphasized that the causative substance is no longer required for the progression of the neoplastic state once it has actually been induced. Nicholson (1950), however, believed that it was impossible to construct a definition and he stated unequivocally that "the reason why these definitions break down lies in the nature of tumours. In no essential character do they differ from the other tissues of the body." Wright (1954) gave an excellent summary of the difficulty when he said: "Definitions, since they represent greater precision of thought, eventually supplant descriptions in science, but until the interrelationships of natural phenomena are clearly understood, the descriptive method of conveying an idea is generally to be preferred."

OCCURRENCE

Man and animals

All the higher animals including fish, amphibia and mammals are prone to develop spontaneous tumours, a conclusion based on a study of animals in captivity. Reference to the early history of experimental cancer reveals the striking variation in animal susceptibility. In 1889, Hanau, using a tar-painting technique, failed to induce tumours in rats. The discovery of tar as an experimental carcinogen was

thus delayed until the success of Yamagiwa and Ichikawa (1915) who used rabbits, and in 1918 Tsutsui obtained similar results with mice. The outstanding feature in a general study of animal tumours is that in all species older animals are predominantly affected (Ratcliffe, 1933).

Age and sex

In man there is a similar age incidence, especially with regard to malignant tumours, though sarcomas occur most frequently in adolescents, while Wilms' renal tumour and adrenal neuroblastoma are confined to infancy or childhood. In the Registrar-General's report for 1938 about two-thirds of the deaths due to malignant disease occurred over the age of sixty years. Apart from tumours of organs peculiar to either sex, some cancers affect one or the other sex predominantly. Cancer of the lip, stomach and lung occur more frequently in men while cancer of the breast, thyroid and gall-bladder show a high percentage in women (Pack and Lefevre, 1930). Cancer of the oesophagus is remarkable in that the post-cricoid variety is almost confined to women whereas tumours of all other parts of the organ show a marked predominance in males.

Socio-economic factors

Cancer of the skin and upper alimentary tract is more prevalent in the lower classes whereas cancer of the lung and rectum is not related to social groups (Peacock, 1956).

Race, diet and personal habits

These three factors are often so intimately connected that they cannot be considered separately. Whereas carcinoma of the uterus appears to be fairly frequent in most races, carcinoma of the breast shows a high incidence in England and America, in contrast to the low rate in Chile and Japan. A comparison of the 1930 birth-rate figures in these countries suggests an inverse relation, the rate in England being 16·3 per 1,000, in Chile and Japan 39·8 and 32·4 respectively (Bogen, 1935). Furthermore, an investigation into lactation in women with carcinoma of the breast revealed that the majority had experienced some difficulty (Lane-Claypon, 1926). This example is, therefore, clearly not an instance of a simple racial factor.

Racial customs play their part in "Kangri" cancer of the abdominal wall seen frequently in tribes in Tibet and on the North-West Frontier of India. As with the "Kang" cancer of the thigh and leg in Chinese, the pathogenesis is that of repeated burning of the skin. Such examples involving an external agent contrast with the internal agent operative in carcinoma of the penis, a disease frequently quoted to illustrate the importance of racial customs. It is very common in the Chinese who are uncircumcised but almost unknown in the Jewish race in whom ritual circumcision at an early age is the rule. It has been demonstrated recently that smegma is carcinogenic to mice (Pratt-Thomas and his colleagues, 1956).

Cancer of the buccal cavity has been studied in this respect in India; in Bombay it was found to account for 36 per cent of all cancers. Betel-nut chewing was associated with cancer of the buccal and other parts of the oral mucosa and individuals who, in addition to chewing, smoked tobacco in the form of hand-made "bidis" tended to develop cancer of the tonsil, base of the tongue, or, less frequently

the oesophagus (Sanghvi and his colleagues, 1955). It is puzzling that smoking "bidis" should be associated with cancers arising in the upper alimentary tract while cigarette smoking is associated with cancers of the lung.

The importance of the calorie value of the diet in relation to the genesis of cancer in animals has been emphasized by Tannenbaum (1954). In animals fed on chronically restricted diets the tumour incidence is strikingly decreased and the time at which neoplasms appear is delayed. Statistical evidence (Dublin, 1954: quoted by Tannenbaum) suggests a similar factor in man as individuals who are over-weight are more likely to die of cancer. General reduction in diet should be clearly distinguished from deficient diets which may give rise to conditions predisposing to cancer. Primary carcinoma of the liver is commoner in coloured races, being in fact the commonest type of cancer in certain Bantu tribes (Berman, 1951) and in the natives of Java (Bonne, 1935). Kennaway's observation (1944) that the disease was rare in American Negroes disposed of the idea that race was the only important factor. Clinical studies (Gillman and Gillman, 1944, 1945) and experimental studies (Gilbert and Gillman, 1944; Gillman, 1944; Gillman and his colleagues, 1945) have shown that the high incidence of liver disease is due to a diet grossly deficient in first-class protein, and in such abnormal livers primary cancer is particularly liable to develop. A high incidence of cancer of the thyroid is reported in areas where goitre is endemic as a result of iodine deficiency (Wegelin, 1928). The frequent association of chronic macrocytic anaemia in women with pharyngeal cancer has led Ahlbom (1936) to suggest that a dietary deficiency may be a common causative factor.

Certain races living in the same country may show a different disease incidence. In Indonesia cancer of the stomach is frequent amongst the Chinese and rare in Javanese (Oberling, 1954). Both races feed on a rice diet but the Chinese use animal fat for cooking while the Javanese use vegetable fat. The possibility of the production of polymers from heating fats in cooking processes such as frying, roasting or grilling, has been given attention. These substances, which are under suspicion as potential carcinogens, are more likely to be formed in cooking utensils made of iron rather than in those of aluminium or glass. Experimental evidence supports this view in that cottonseed oil, heated to 320°C. in the presence of iron, is a more potent carcinogen for the fore-stomachs of mice than the same oil heated in glass vessels (Peacock, 1956).

The possible influence of water on the incidence of gastric cancer was studied by Stocks (1947) and a higher incidence was found in areas supplied by river water than in those drawing water supplies from wells. In Holland, Diehl and Tromp (1954) reported the highest total cancer death-rate for all sites in municipalities supplied by river water with a low manganese content. Conversely, further studies showed lower cancer frequencies where the manganese content of the drinking water was high. These results stimulated an investigation into the possible relationship existing between the geology of soil and the incidence of cancer (Tromp and Diehl, 1955).

Statistical evidence seems to have established an association between cigarette smoking and lung cancer. Attempts to isolate a causative agent have included an investigation into the temperature in the combustion zone of a cigarette (Lyons, 1955; Ermala and Holsti, 1956). At the average range of 650°C. obtained, carcinogenic hydrocarbons are formed from organic matter, and some workers have

detected benzpyrene in cigarette tar (Commins, Cooper and Lindsey, 1954; Cooper and Lindsey, 1955; Lyons, 1956). The amount of benzpyrene detected is remarkably small when compared with that present in the atmosphere of industrial areas and it is difficult to accept it as the causative agent. Ordinary atmospheric pollution cannot be excluded and many investigations into the constituents of the atmosphere in industrial areas have been carried out. At the present time Peacock is conducting an animal experiment in which colonies of mice are being maintained in filtered and unfiltered air; his results are awaited with interest. Kennaway and Urquhart (1952) have shown that the arsenic content of air in industrial areas is three-and-a-half times greater than in the country, and it is noteworthy that arsenic in American cigarettes has increased by 300 per cent as a result of its use in pest control (Satterlee, 1956). The role of arsenic in carcinogenesis has been reviewed by Currie (1947) and Neubauer (1947), and it is significant that Hill and Faning (1948) found a relative increase of cancer both of the skin and respiratory tract in a group of workers exposed to inorganic arsenical dust.

Radiation hazards

Radiations of various types are known factors in the causation of skin cancer. Melanin appears to afford some protection against chronic exposure to ultra-violet light, and thus coloured races are much less likely than are white races to develop skin tumours such as squamous-cell and basal-cell carcinoma.

The part played by radiation in inducing malignant tumours was recognized when some of the earlier x-ray workers developed cancer of the hands and face. The importance of radioactive materials was emphasized by Martland (1931) who described cases of osteogenic sarcoma occurring in girls painting luminous dials with material containing small amounts of radium and mesothorium. These substances, which were absorbed from the mouth as the girls pointed the brushes by putting them to the lips, became deposited in the bones where the radioactive effect persisted and induced malignant tumours. The likelihood of a similar problem arising in connexion with radio-strontium is now being discussed. In recent tests of nuclear weapons one of the fission products present in considerable amount in the fall-out is radioactive strontium. This substance may be deposited on foliage whence it can be absorbed either by the plant itself or by a grazing animal. It may then reach the human body and if absorbed becomes deposited in the bones. This radioactive element has a long half-life of 28 years and its persistence is a problem which merits serious consideration.

Recently the general question of radiation hazards has been widely discussed and two important publications have resulted in America and in Great Britain (United States Atomic Energy Commission, 1955; Medical Research Council Special Report, 1956). The American contribution is interesting as it is the first official account of the fall-out to be expected from explosions of hydrogen bombs. The Medical Research Council's Report has a more general approach and includes a consideration of the dangers of increased genetic mutation. The radiation dose to the gonads has been calculated and it is likely that man has increased this dose by at least 25 per cent in the last 50 years by the use of ionizing radiation. Apart from the background dosage from natural sources it was estimated that an additional 22 per cent was contributed to the general population by diagnostic radiology. This surprising finding calls for a review of current practice, with attempts to limit

the number of examinations in the regions of the lower abdomen and pelvis especially in young people. The importance of diagnostic radiology as a hazard has been underlined by a study of children who died of leukaemia or "other malignant disease" (Stewart and her colleagues, 1956). It was found that approximately twice as many of the mothers of these children had been examined radiologically during pregnancy as compared with those in a control group. The association of leukaemia with radiotherapy given for ankylosing spondylitis has also been reviewed (Court Brown and Doll, 1956) and the connexion definitely established. Studies of cases of thyroid cancer in whom the neck or chest region have been irradiated in infancy for thymic enlargement suggest that a similar association may be present (Duffy and Fitzgerald, 1950; Clark, 1955; Simpson and his colleagues, 1955).

Industrial hazards

With the development of modern industrial techniques, occupational hazards are constantly increasing. Since Percivall Pott described cancer of the scrotum in chimney sweeps in 1775, occupational cancers in that region and on other parts of the skin surface have been reported. Malignant tumours appear at the sites exposed to the carcinogens, in most cases either mineral oil, tar, pitch or creosote. The substance must have access to the skin for a long period and malignant tumours rarely develop in less than five years. It is even more surprising that they may appear several years after contact with the carcinogen has ceased (Henry, 1947).

A higher incidence of bladder cancer in coal gas, tar, and pitch workers than in the general population seemed likely (Henry, Kennaway and Kennaway, 1931) but it was in the dye industry that the disease became established as an occupational hazard. Experimental work on dogs led Hueper and his colleagues (1938) to conclude that 2-naphthylamine rather than aniline was the carcinogen. The problem has been studied by implantation of suspected carcinogens into the mouse bladder (Bonser and her colleagues, 1951) and it has been found that tumours can be produced by a hydroxyamine (2-amino-l-naphthol) which is known to be excreted in the urine of dogs fed with 2-naphthylamine (Bonser and her colleagues, 1952). As 2-naphthylamine is non-carcinogenic when introduced into the bladder (Jull, 1951), Clayson (1953) has suggested that aromatic amines are carcinogenic to the bladder by virtue of their conversion in the body into orthohydroxyamines.

For many years arsenic was suspected as being the causative agent in the industrial cancers discussed above. This has now been disproved, but it is recognized as being carcinogenic to man althougn all attempts at tumour induction in animals have been unsuccessful. Skin cancer is known to occur in sheep-dip workers who are exposed to arsenical dust; it is also seen in certain skin diseases, such as psoriasis, which have been treated with medicinal arsenic for long periods. Arsenic was the only known non-radioactive inorganic carcinogenic substance until Gregorius (1952) noted the high incidence of lung cancer in chromate workers. Beryllium salts, used extensively in the preparation of fluorescent lighting tubes, were known to cause granulomas in man, and intravenous injection of a mixture of these salts has produced osteosarcomas with metastases in rabbits (Dutra, 1949; Dutra and Largent, 1950). Rabbits kept in a dusty atmosphere containing beryllium developed osteogenic sarcoma (Dutra, Largent and Roth, 1951) and,

although no similar occurrence has been recorded in man, this observation draws attention to yet another industrial hazard to which beryllium workers may be subject.

The introduction of radioactive elements into the chemical industry and the artificial production of radioactive isotopes has opened up a new set of hazards. Experimental proof of the carcinogenic action of these substances has been obtained; malignant fibrosarcomas have been produced in mice using only 1 microgram of plutonium (Lisco and his colleagues, 1947). When it is realized that there are 43 industries involving the use of crude tar, 50 the use of chromates, and 72 the use of inorganic arsenic, the full impact of industrial factors on modern medicine will be appreciated.

This subject is also dealt with in Volume 1, Chapters 11 and 12.

STRUCTURE AND BEHAVIOUR

Nature of neoplastic cells

The cells of a benign tumour are often almost identical to those of the organ in which they arise. Of malignant tumours, those that are differentiated show varying degrees of similarity; undifferentiated types bear little or no resemblance to the parent tissue. Differentiation and growth rate, as indicated by cellularity, usually vary inversely, and are factors of practical value in the histological assessment of the nature of tumours. The safest diagnostic criterion of malignancy is the invasion by neoplastic cells of neighbouring structures; for example, fat in carcinoma of the breast, and muscle in alimentary carcinoma. When this is seen the diagnosis is not in doubt. In the earlier stages of the development of a malignant tumour, before local infiltration has occurred, the assessment can only be made on the actual appearances of the malignant cells. This difficulty has been emphasized in the newer techniques of exfoliative cytology. For instance, in the examination of sputum for cancer cells, isolated malignant cells must be recognized divorced from their surrounding structures. As a result it is now realized that there is no known absolute distinguishing feature between normal and malignant cells. The latter tend to be irregular in size, shape and staining reaction. If growing rapidly they may show hyperchromatism with an increased number of mitotic figures. It is well known that the histological appearances of granulation tissue may bear a striking similarity to some sarcomas, whilst cellular irregularity and numerous mitotic figures near an infected and ulcerated surface may be reminiscent of early malignant change.

Exfoliative cytology has been used to diagnose cancer of epithelial surfaces (Figs. 1, 2 and 3) such as the bronchus and the cervix uteri (this subject is considered in Vol. 3, Chapter 24). It is particularly useful in detecting early cases in which the lesion is minute and tissue invasion absent or minimal. This condition is known as "carcinoma *in situ*"; its diagnosis depends on the recognition of isolated cancer cells in the secretion of the part.

It was hoped that the development of biochemical techniques might reveal some chemical difference in malignant cells but such changes as have been found are quantitative rather than qualitative. Some workers believed that an abnormal cellular enzymic content was responsible for tumour growth and detected excessive

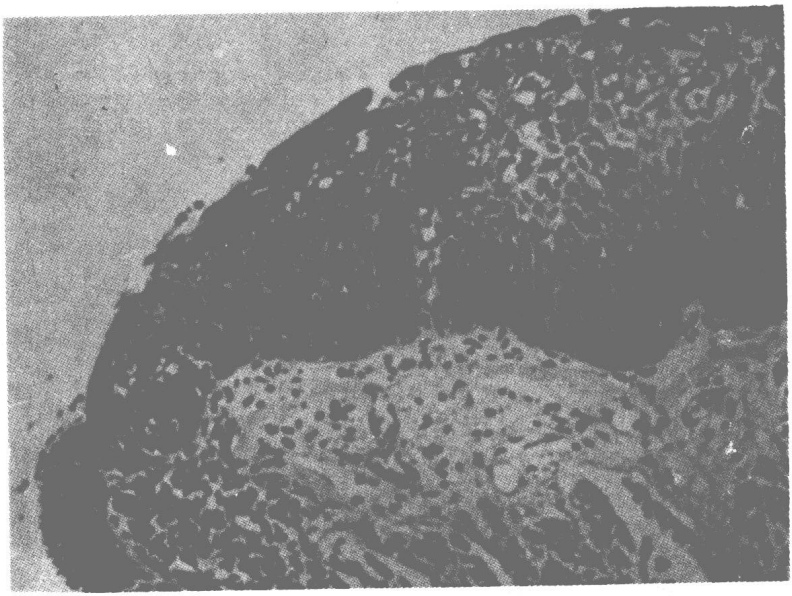

FIG. 1.—Carcinoma *in situ* in the main upper lobe bronchus. The transformation from normal ciliated epithelium is clearly seen at the left lower edge of the picture. (x 150.)

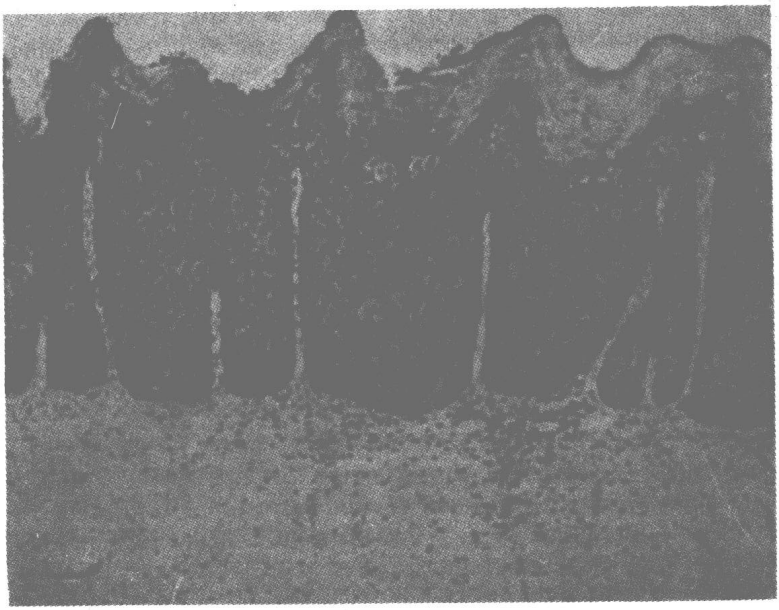

FIG. 2.—Photomicrograph showing the characteristic cellular irregularity of an area of carcinoma *in situ* developing in the cervix uteri. (x 100.) (*Reproduced by courtesy of Dr. John Beattie.*)

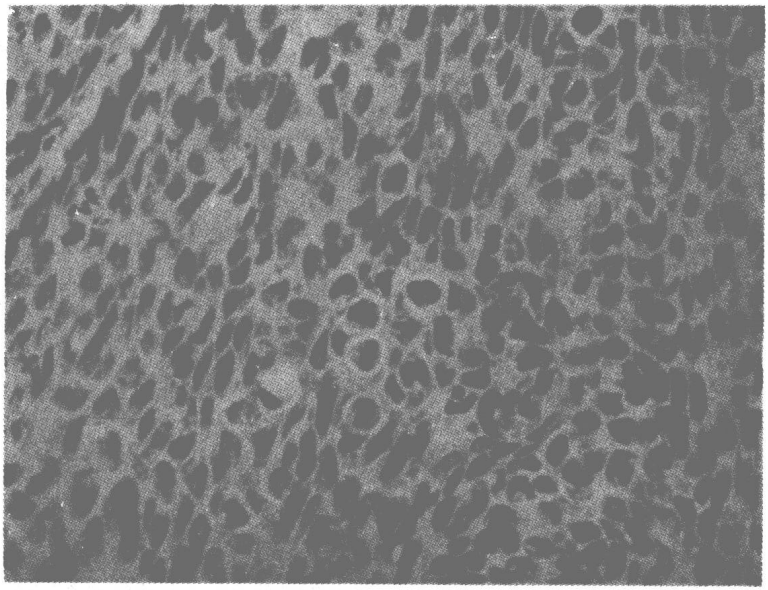

FIG. 3.—High-power view of the photomicrograph in Fig. 2 to show cellular detail. Note the presence of numerous mitotic figures. (x 350.) (*Reproduced by courtesy of Dr. John Beattie.*)

quantities of certain enzymes in the urine of cancer patients. In other cases a high content of mucoprotein has been found in the serum and the urine (British Empire Cancer Campaign Report of 33rd Annual Meeting, 1955). Many attempts have been made to discover a diagnostic test for cancer in its early stages, using serum or urine, but lack of specificity of such tests has served to emphasize that, as far as is known, the metabolism of cancer tissue is in no way unique and probably closely resembles that of the parent tissue. Many years ago Warburg (1930) stated that cancer cells differed in that they produced glycolysis anaerobically but Berenblum and his colleagues (1940) showed that certain non-neoplastic tissues also possessed a similar glycolytic mechanism. In 1956, Warburg claimed to have put the relationships of anaerobic glycolysis and respiratory defect on a quantitative basis. By using mouse ascites tumour he found that the differences between cancer and normal cells is much greater than had been previously considered. These experiments are open to criticism on the grounds of the technical difficulty of making a comparison between a mass of neoplastic cells and a portion of normal tissue with a well-developed stroma.

Wright (1928) cultivated malignant cells *in vitro* in media exposed to different gas mixtures containing varying proportions of oxygen. Under these conditions mitosis was found to cease before total anoxia was reached. In recent years it has been reported that malignant change has been induced in cells in tissue culture (Earle, 1942, 1943) and Goldblatt and Cameron (1953), growing normal cells under intermittently anaerobic conditions, claim to have brought about malignant change. It should be noted that in all cases there was no definite malignant transformation *in vitro*; it was only on injection of the material into other animals that malignant tumours were induced.