tion at any time, either then or subsequently, is to be avoided if there be any suspicion of pulmonary abscess in addition to the empyema.

In *autopyotherapy* the limit of hopefulness in conservative treatment would seem to be reached; and even the recorded success in one case of injecting 1 c.cm. of the pus subcutaneously, at intervals of four or five days, seems scarcely to justify the employment of the practice as a general method of treatment.

The importance of treating the patient must never be lost sight of. Indeed, the after-care of the patient should receive special attention. Abundant aërotherapy should be adopted, and, whenever possible, the patient should be in the open air for long periods of the twenty-four hours. The diet should be simple. Sunlight or/and ultra-violet rays are often helpful. The use of vaccines, though not so popular as a decade or two ago, should be considered, and general tonic measures are not to be omitted. In this way is combated any residual infection that may exist, and expansion of the lung is encouraged. Respiratory gymnastics—deep breathing—may well be employed, and

less caution is necessary here than in serous effusions, lest such helps be sought too early.

The problem of the residual sinuses is oftentimes a difficult one. The help of x rays and lipiodol injections is notorious. The indications for treatment when the case has arrived at this point depend upon the application of two principles: that a septic focus in the chest, however small, constitutes a general as well as a local danger; and that there are only two ways in which such a focus can be effectively dealt with—either the lung must be allowed to expand until it reaches the chest wall, or the chest wall must be allowed to fall in until it comes in contact with the lung. Which of these two modes of securing permanent healing is chosen, or whether both are chosen, depends upon the particular case. In the first instance digital exploration with efforts at decortication is the method of election; in the latter, the resection of portions of more ribs. Meantime the methods by which the patient's general tone is re-established must not be relaxed. In such difficulties patience, vigilance, and the pursuit of the principles stated usually achieve the end desired.

An Address

ENTITLED

LYMPH-STASIS THE PRECURSOR OF CANCER.

DELIVERED AT WELLINGTON BEFORE THE NEW ZEALAND
BRANCH OF THE BRITISH MEDICAL ASSOCIATION,
FEBRUARY 19TH, 1929,

BY

W. SAMPSON HANDLEY, M.S., F.R.C.S.,
SURGEON TO THE MIDDLESEX HOSPITAL AND TO THE MIDDLESEX
CANCER HOSPITAL.

(With Special Plate.)

I PROPOSE to use my opportunity to-day for the purpose of laying before you my views on the origin and causation of cancer. Carry your minds back, then, to the dawn of the world, uncounted millions of years ago, when life first appeared upon its surface in the form of amoeba-like organisms, each a single cell, a single unit of living protoplasm, animated by two fierce passions—the desire for food and the desire to double its ego by the simple process of cell-division.

A little later in time there arose from these unicellular organisms, organisms composed of many cells living together in a communal life like that of a small village or a great city. The cells are now specialized into groups, and each kind of cell follows a trade or profession, exerting for the community its special skill, receiving from the community in exchange food, warmth, and protection. To carry out the scheme and to ensure that each cell receives its due share of food, and of such cell products as it no longer makes for itself, elaborate systems of conduits—the circulatory, lymphatic, and glandular systems—have been evolved, and equally elaborate machinery, comparable with the telegraphs, telephones, and newspaper and business offices of the city, brings information of the outer world, and controls the activities of the cell community. As Sir Arthur Keith¹ has said: "The resemblance between the body physiological and the body politic is more than an analogy; it is a reality," and Mr. Morley Roberts² has insisted that politics must be regarded as a branch of the science of biology.

It is a part of the bargain that the individual cells shall abandon the primitive right to unlimited cell division. In the many-celled animals this right is reserved to the cells of the ovary and testis.

THE ORIGIN OF MANY-CELLED ORGANISMS.

It is an interesting speculation how the many-celled organisms arose from the unicellular individuals, which were presumably the first living things to appear on the globe. It appears likely that they arose from some inhibition of the process of cell division when it had proceeded half-way—that is to say, the nucleus completely divided,

but the cell protoplasm still remained connected by protoplasmic strands. There is evidence that the cells of the higher animals are still interconnected by protoplasmic bridges.

To understand the origin of multicellular organisms the most hopeful avenue is a study of the processes which inhibit or frustrate cell division after the process has been initiated. Such a study might be pursued upon the amoeba.

Note that, if the foregoing sketch of evolution is true, each cell of one of the higher animals is descended from a primitive one-celled organism with an irresistible appetite for food and for multiplication. Note, further, that these are the appetites which dominate the cancer cell, and you may be led to conclude that cancer is an atavistic reversion of certain cells of the body to the state of their primitive one-celled ancestors. Such a conclusion would, in my opinion, be correct. The cancer cell is a selfish unicellular organism, derived by direct descent from the cells of the body, but living among them as a parasite.

You might further be led to compare the cancer cell, with its fierce antisocial individualism, to an anarchist in the body politic, and to inquire whether the anarchist represents a spontaneous reversion to the savage primitive type of man, or whether he is the product of disorders in the social organism. Experience shows that the anarchist does not appear, or is soon exterminated, in prosperous and happy communities. It is therefore probable that in cancer the reversion to the primitive cell type is conditioned by disordered bodily function. In other words, the body has failed to carry out the contract under which the cell abandoned its right to unlimited multiplication. Under that contract each cell of the body has the right to its share of the products of all the other cells. It has also a right to protection from external irritation. It is my object now to show how the contract has been violated. My observations lead me to believe that the origin of cancer is intimately associated with local obstruction of the lymph vessels in the area where the cancer arises. To produce cancer the obstruction must be of long standing—must have lasted from twenty to thirty years. It may not be complete enough to cause obvious lymphatic oedema, but may manifest itself only by papillary hypertrophy and increased cellularity of the subepithelial connective tissues.

Complete direct proof of this theory is at present impossible. But if the disconnected heap of jig-saw fragments which constitute our knowledge of cancer are tried together upon this hypothesis and are found to fit as a coherent picture, a definite orientation, hitherto lacking, will be given to experimental work on the origin of cancer. It is for the reader to judge if my work fulfils the object thus stated.

It is, I think, significant to note that the recent work of Warburg shows that the cancer cell is a cell which has somehow acquired an entirely new type of cell metabolism, but no suggestion has hitherto been offered as to the way in which this change of cell habit is brought about. It is

evident that chronic lymphatic obstruction must profoundly influence the conditions under which the cell lives. The intercellular pressure must be raised, wandering cells brought by the blood will be trapped in the district and will be unable to leave it, the supply of oxygen will be restricted, and the fluid bathing the cells will be relatively stagnant—wanting, therefore, in the supply of fresh hormones derived from other cells of the body, which it should normally contain, and wanting specially in the inhibitory hormone which is the sedative to the cell's primal passion for division.

We must now consider what light can be obtained upon the etiology of the disease from a study of experimentally produced cancer. The salient facts will be found well marshalled by P. Menetrier,³ who has himself done so much to advance this subject. He shows that attempts to induce cancer by the injection of micro-organisms, or by the inoculation of embryonic grafts, have failed. Doubt is thus thrown upon the infective theory of cancer, and upon Cohnheim's hypothesis of its origin in embryonic "rests." On the other hand, chronic irritation in various forms has succeeded in artificially inducing cancer; and Menetrier's belief that cancer is a morbid process resulting from "multiple and non-specific forms of irritation" is thus justified. The successful irritant may be:

1. A physical agent, such as α rays, radium, or heat.
2. A chemical agent, such as tar or paraffin.
3. A parasitic agent, such as the spiroptera which causes stomach cancer in rats, and possibly the bilharzia (bladder cancer) and the demodex (Borrel).

It must be observed in passing that it does not take us far to say that chronic irritants produce cancer. We want to know whether their effect is a direct one on the epithelium, or is exerted indirectly through an action upon the connective tissue. If the latter, what is the nature of the connective tissue change?

To resume our study of Menetrier. By exposing the ears of guinea-pigs for long periods to repeated small doses of α rays he produced hyperplasia of the epithelium and metaplastic alterations of the cells. He draws attention to the great thickening of the epithelium, and to the formation in it of cell nests, also to "papillomatous appearances," which he evidently considers deceptive and due to the downgrowth of epithelial processes, a mistake which Clunet also made. He does not refer to the changes in the connective tissue of the papillae.

In concentrating his attention upon the epidermic changes and ignoring those in the connective tissue, I believe that Menetrier has missed the true interpretation of his results.

In his figure (Fig. 9) there are to be seen hypertrophied papillae, a stage of real if incipient papillomatosis. In the centre of each of the two hypertrophied papillae on the left are seen cellular cords, uniting below to form a single vessel. My experience with lupus (cf. Fig. 7) warrants me in asserting that these cords are papillary lymphatics of origin in a state of proliferative lymphangitis. In the papillae to the right of the figure the process has gone further: the vessels have been destroyed and a richly cellular mass of granulation tissue has replaced them (cf. Fig. 8). In my view, then, the α rays have set up an obliterative lymphangitis of which the epithelial hypertrophy is a secondary consequence. A direct stimulating action of the α rays upon the epithelium may no doubt occur, but it is of less moment than the lymphangitis which Menetrier ignores, as will be seen when the facts of lupus carcinoma are studied.

Marie, Clunet, and Lapointe exposed a number of white rats to a few successive massive doses of α rays, each dose causing a severe dermatitis. In two cases a spindle-celled sarcoma arose in the irradiated area, but epithelioma was not produced in any of the animals. These experiments, from my point of view, show the predominance of the connective tissue changes produced by chronic radiation over the epithelial changes. Though in man the epithelial changes may ultimately prove of more serious import, they are conditioned by previous long-standing chronic lymphangitis, and perhaps to a less extent by obliterative haemangeitis.

It may be remarked that papillomatous hyperplasia is a recognized precursory stage of α -ray cancer. Further-

more, early α -ray epitheliomata have a tendency to remain localized for a long time, and only disseminate when they have advanced by infiltration into regions where the lymphatics are still intact. In these respects they resemble lupus cancer, which is certainly conditioned by lymphatic obstruction.

In 1923 Block succeeded for the first time in producing an α -ray carcinoma in a rabbit.

TAR CANCER.

The precancerous stage of clinical tar cancer manifests itself by the production of warts (Fig. 11), which mostly after a time drop off, leaving an erythematous or pigmented patch. Sooner or later one of the warts grows, becomes broad-based, ulcerates, and develops all the signs of malignancy (Fig. 12). Yamagiwa and Ichikawa in 1914 first succeeded in producing experimental tar cancer by painting the ears of rabbits with coal-tar once every two or three days. Sometimes the applications were preceded by the intradermic injection of scarlet-red, an admirable means of irritating the lymphatic vessels. In from 30 to 100 days papillomatous new formations appeared. In certain cases after 55 to 360 days carcinoma appeared. In a later series of experiments carcinoma was produced in 77 per cent. of the experimental animals. In 72 per cent. metastases occurred. The same authors injected tar into the mammary gland of female rats, and produced cancer of the mamma in 12 per cent. of the animals. Yamagiwa and Ichikawa state that "repeated simple chemical and physical irritation renders the normal epithelial cell cancerous, without any necessity to invoke another unknown causal agent." This statement requires examination. It is at least possible that the tar acts primarily upon the connective tissues, and we must now inquire into the evidence available upon this point.

It is certain, at any rate, that the connective tissue is not indifferent to the irritation of tar, for in Fibiger and Bang's experience, out of 24 tar carcinomas in mice, 2 were accompanied by a tar sarcoma. Russell produced sarcomas by deep or subcutaneous injections of tar.

More direct evidence of the importance of the connective tissue changes produced by tar painting comes from Borrel. He noted the accumulation of connective tissue cells (mastocytes) forming little intra-epidermic or sub-epidermic collections. Prolongations from these mastocytes insinuate themselves between the cells of the Malpighian layer, which is thus dissociated. The observations of Borrel harmonize with those of Victor Bonney,⁴ who in every case found that the origin of a cancer is preceded by increased cellularity of the subjacent connective tissue. Menetrier, without, I think, sufficient reason, ascribes these collections of connective tissue cells rather to accidental infections of the skin than to the action of the tar. Nevertheless, Menetrier himself, in the epithelial hypertrophy of the hair follicles, which is one of the precursory stages of tar carcinoma, observed a great increase in the number of branched pigmented connective tissue cells (chromatophores) lying among the deeper layers of the epithelium and in the superficial layer of the dermis. Evidently in such cases a powerful stimulus has been applied to the connective tissue.

In the other precancerous stage of tar carcinoma, that of papillomatous hypertrophy, the deeper layer of the epithelium shows a hyperplasia of the chromatophores (pigment-bearing connective tissue cells) which it normally contains. Later an increase of chromatophores is seen also in the underlying dermis.

It must, however, be admitted, as Menetrier insists, that in the rabbit's ear the onset of tar carcinoma may occur in the absence of any connective tissue proliferation. It is true, as Menetrier says, that this fact runs contrary to the views of Ribbert as to the importance of inflammation of the connective tissues in the origin of cancer, but, on the whole, the balance of evidence points strongly to the view that the action of tar is primarily upon the connective tissue. I suggest that tar produces cancer by causing lymphatic obstruction with papillary hypertrophy as an intermediate stage in the process.

It has long been known that the evolution of a papilloma into a carcinoma is not a rare event, but the closeness of

FIG. 1.—Cross-sections of skin papillae in Paget's disease of the nipple, showing blocked central lymphatics.

FIG. 2.—Cross-sections of skin papillae in lupus, showing blocked central lymphatics. (Cf. Fig. 1.)

FIG. 3.—An innocent duct papilloma of the breast. (Contrast Fig. 4.)

FIG. 4.—A duct papilloma of the breast which is already carcinomatous. (Contrast Fig. 3.)

FIG. 5.—A highly magnified portion of the papilloma seen in Fig. 4, showing infiltration of its connective tissue by malignant epithelium.

FIG. 6.—Hypertrophied papillae adjacent to a carcinoma of the tongue. On the right the edge of the carcinoma is seen.

FIG. 7.—Section just beyond the edge of an area of non-ulcerative lupus of the skin, showing the blocked papillary lymphatics which simulate a stag's antler in outline.

FIG. 8.—A much hypertrophied papilla of the skin in lupus occupied by tuberculous granulation tissue and by a line of giant cells representing the original central lymphatic.

FIG. 9.—Epithelial hyperplasia and metaplasia in the ear of a rat following x-radiation. From Menetrier, *Le Cancer, Généralités*, p. 129.

FIG. 10.—Lupus carcinoma of the left cheek. On the right cheek is seen an innocent papilloma.

FIG. 11.—Tar warts of the forearm. From a patient who had worked in hot tar for twenty years.

FIG. 12.—The scrotum of the same patient, showing a tar carcinoma.

the relationship between these two forms of tumour has only very recently been realized. It seems probable that carcinoma is invariably preceded either by a definite papilloma or by a local area of papillary hypertrophy.

Chronic glossitis with papillary hypertrophy is the usual precursor of carcinoma of the tongue (Fig. 6). Cancer of the lip and of the larynx frequently arises on a pre-existing papilloma.

In regard to carcinoma of the stomach there is no evidence.

Cuthbert Dukes⁵ has shown that in the neighbourhood of early carcinoma of the large bowel groups of papillomata can be usually demonstrated, though these disappear at a later stage (Fig. 13a). He infers that carcinoma of the bowel begins as a papilloma. Cases of multiple papillomata of the colon are known to end almost invariably in carcinoma, and generally before middle age is reached (Fig. 14). Dukes has been able to demonstrate the origin of carcinoma at the tip of a papilloma (Fig. 15). On two occasions I have seen a papilloma appear at the lip of a colostomy opening as a little stalked, perfectly innocent, tumour, and develop within a few weeks into a carcinoma. On the first occasion, in a case of abdomino-perineal excision of the rectum for carcinoma, the new primary carcinoma grew rapidly and produced a malignant stricture of the colostomy opening. On the second occasion I excised the incipient carcinoma with scissors. It was the earliest and smallest carcinoma I have seen, and resembled Fig. 14.

MULTIPLE PAPILLOMATA OF THE LARGE BOWEL.

Jüngling⁶ has supplied a remarkable family tree covering four generations descended from a male who died of pulmonary tubercle and a female who died of old age. Both the ancestors were free of polyposis. Of their thirty-one descendants, fourteen suffered from polyposis of the alimentary tract, five from cancer of the rectum. Two of the first generation died of intestinal tubercle. Four of the six children of the first generation died of carcinoma of the rectum. For further details the family tree must be consulted. It appears to justify Jüngling's assertion that the tendency to polyposis behaves as a Mendelian dominant.

Professor Jüngling makes no comment on the fact that this family had a tuberculous ancestor and that tubercle

reappeared in the two succeeding generations. Yet it seems to me likely that this fact is the key to the unknown pathogenesis of intestinal polyposis. It is known that

when tubercle attacks the skin it may cause either an ulcerative or a warty non-ulcerative form of lupus. I believe that when it attacks the mucosa of the intestine, and fails to produce ulceration, an intestinal polyposis is the result.

And just as carcinoma may attack the scarred area of a lupus, so may it arise in an intestinal polyposis. Papilloma of the bladder likewise, in my opinion, is a non-ulcerative form of tubercle of the bladder. A case in which I removed a typical polypus from near the right ureter, and had subsequently to remove the right kidney for what proved to be advanced tubercle, remains in my mind as a probable indicator of the pathogenesis of vesical polyposis.

It might appear useless to bring forward these hypotheses upon such inadequate evidence. I do so in order to suggest that some young investigator who reads these lines should endeavour to produce intestinal and vesical polyposis in animals by injecting the lymphatics locally with a suspension of active tubercle bacilli.

CANCER OF THE BREAST.

In the case of the breast the appearance which Lenthal Cheatele calls the "laciform edge" is a diffuse papillomatosis of the smaller ducts. He points to this appearance as a precursor of malignancy. If, as Cheatele maintains, and I think correctly, nearly every case of breast carcinoma originates in the ducts, it is probable that nearly every case of breast cancer is preceded by papillary hypertrophy or by definite papillomata.

Duct papilloma of the breast is recognized clinically when it arises in the larger ducts and causes serous or blood-stained discharge from the nipple. Such cases, if neglected, are known to end usually in carcinoma. In the following case I was able to demonstrate the occurrence of carcinomatous degeneration in a duct papilloma of the breast, which had apparently only existed for a very

short time. At the time of the operation the papilloma was suffering from carcinoma, but the disease had not yet attacked the tissues of the patient herself.

Mrs. —, aged 70, noticed a serous discharge from the left nipple a week before she was first seen on June 12th, 1928. The breast was normal on palpation except that, vertically half an inch below the left nipple, a tiny very superficial shot-like swelling could be

FIG. 13.

FIG. 13.—Portion of colon removed by operation from a case of multiple adenomata. Note the little round tumours scattered over the mucous membrane. (M.A. 5.) ($\times 2$). (Dukes.)

FIG. 13a.

FIG. 13a.—To show the naked-eye appearance of the simple tumours associated with a cancer of the rectum. (Dukes.)

FIG. 14.—A complete section through a very early cancer of the rectum, which measured only 1 cm. in its broadest diameter and projected like a little button about 3 mm. above the surface of the bowel. Four small non-pedunculated adenomata were found within a radius of two inches of the growth. (M.A. 6.) ($\times 8$). (Dukes.)

FIG. 15.

FIG. 15.—A polypoid adenoma situated close to a large ulcerating cancer of the rectum, but separated from it by an inch of normal mucous membrane. Other smaller adenomata were also present. The cells at the tip of this tumour had undergone cancerous degeneration (A) (see Fig. 15a); B, lymphoid follicle in stalk of tumour (dark mass). (M.A. 9.) ($\times 6$). (Dukes.)

FIG. 15a.

FIG. 15a.—A higher magnification of the tip of the polypoid adenoma illustrated in Fig. 15, to show onset of cancer at tip. ($\times 135$.)

felt. Pressure at this point made fluid exude from the nipple. No other nipple changes were found. There were no glands in the axilla. On June 15th, 1928, this lump was cut down upon, two dilated ducts were exposed, divided close to the nipple surface, and then again divided where they began to ramify in the breast substance. On section of the excised portion across the ducts a small papilloma, just visible to the naked eye and perhaps one-fiftieth of an inch in diameter, was found within the duct, attached to it by a slender pedicle. A section across the tissue showed that this minute and early morphological papilloma had already become a carcinoma within its own substance. The fibrous tissue of its core was infiltrated with carcinoma cells, though there was no evidence that the physiological tissues of the patient had been attacked by the disease. The pedicle of the papilloma, fortunately included in the section, was composed of fibrous tissue only, and showed no infiltration. (Figs. 4 and 5.)

An indication of the pathogenesis of the papilloma was, however, given upon examination of the pedicle. It showed several cylindrical groups of round-celled infiltration, some cut as circles, others as ovals. In company with one of the groups was a small artery. These are exactly the appearances given by blocked lymphatics which have lost their lumen by proliferation of their endothelium, as I know from my experience of lupus and elephantiasis. In other words, the patient had suffered from a chronic lymphangitis of the tissues of the breast, and it appears highly probable that the resulting lymph-stasis was one of the main exciting causes of the papilloma which so rapidly developed into a potential carcinoma. It appears possible that the *Demodex folliculorum*, known by the work of Dr. Helen Chambers and others to be so common an inhabitant of the nipple and of the terminations of its ducts, is competent to excite mild infections and abrasions of the nipple, which, while causing no clinical symptoms, may nevertheless set up a chronic lymphangitis.

By this time you will, I think, admit that a process of papillary hypertrophy, sometimes only to be shown microscopically but often producing visible warts or papillomata, is the characteristic precursory stage of carcinoma. Chronic irritation, whether it be bacterial or chemical, would appear to be a cause of cancer, because it is a cause of papillary hypertrophy. If this be so, a study of the origin of a papilloma may be the key, and at least must be an essential preliminary to an understanding of the genesis of carcinoma.

THE PATHOGENESIS OF THE PAPILOMA.

If a single papilla of the skin or of a mucous membrane is examined it is found to consist of a teat-like elevation of the connective tissue carrying in its substance a mesh-work of blood capillaries. These capillaries are supplied by an arteriole and drained by a venule. The papilla is clothed by a covering of epithelium, and it has always been presumed by the dermatologists that the active agent in the formation of a papilloma is increased proliferative activity on the part of the epithelium, and that the increase in size of the connective tissue papilla is merely a response to increased nutritive demands from the active epithelium. Unna, on these grounds, objected to the word "papilloma," and wanted to substitute for it the word "acanthoma," as indicating an innocent tumour of the prickle epithelium. He ignored an essential anatomical element of the papilla which is the key to its normal and morbid physiology. The central structure of every papilla of the skin or the mucous membrane is a lymphatic capillary exactly like the lacteal vessel of a papilla of the small intestine. I have demonstrated this by direct lymphatic injections of the skin, as well as by a study of diseases affecting the skin lymphatics (Figs. 1 and 2). Papillary hypertrophy occurs, and I believe only occurs, when this central lymphatic vessel of the papilla is blocked. The papilla is a little physiological engine. From its blood capillaries there exudes into its connective tissue spaces a constant nutritive stream of diluted blood plasma at a certain pressure. The excess of fluid is renewed and the equilibrium maintained by the drainage action of the central lymphatic. Block this lymphatic and what will happen? The first effect will be a rise in the pressure in the intercellular spaces of the papilla, and on ordinary hydraulic principles the papilla will increase in size until the intercellular pressure is equal to the pressure in the capillary blood vessels. A second effect will be over-nutrition and consequent proliferation of the papilla itself and of the overlying epithelium. But the most important effect of

all for our present purpose remains to be considered. In the normal papilla a constant stream of blood fluid, along with lymphocytes, is exuding from the capillaries and passing away by the lymphatic. As soon as the lymphatic is blocked, stasis occurs and the flow of fresh blood fluid through the papilla is arrested or greatly retarded, even though just as much blood may be passing through its blood capillaries. Two consequences are inevitable: the supply of oxygen to the tissues of the papilla, to its epithelium as well as to its connective tissue, will be much reduced; furthermore, the supply of hormones to the cells of the papilla will be cut off or greatly diminished. In this connexion I use the term "hormone" perhaps somewhat loosely, to signify those products of the rest of the cells of the body which are necessary to the well-being of the cells of the papilla we are considering. Here, I think, we approach the crux of the problem.

Local lymphatic stasis brings about a definite rupture of the contract in virtue of which the unicellular organism originally forswore its egotism and became a social unit. Or, in the terms of biochemistry, the epithelium covering the papilla is deprived of the supply of growth-inhibiting substance, which in a well-conducted cell community is circulated to every cell.

I have shown that local lymphatic obstruction must seriously reduce the supply of oxygen to the epithelium of the blocked papilla. It would not be surprising if, in the course of years, the affected epithelium, adapting itself to meet this difficulty, should acquire a type of metabolism in which oxygenation played a relatively subordinate part. Warburg has recently brought forward strong evidence that the carcinoma cell, as compared with the normal epithelial cell, is an anaerobe, deriving most of its energy from the hydrolysis of sugar into lactic acid, and relatively little from oxidation. This remarkable fact is in exact accord with the theory of the origin of cancer which I am presenting to you. It must not be forgotten that in dealing with such a complex matter as the origin of cancer, direct proof is, in the earlier stages, not to be expected. All that can be hoped is to fit together the isolated facts into a coherent pattern.

In only one variety of cancer can I present with absolute clearness to you all the stages from the initial obstruction to fully developed carcinoma, a cycle of changes occupying in the human subject from twenty to thirty years. Tuberculous lupus, especially of the non-ulcerative variety known as lupus erythematosus, is followed, in a certain proportion of cases, by the appearance of warts upon the scarred surface, and one or more of these warts may develop into carcinoma (Fig. 10). Lupus carcinoma has been stated to be an x-ray carcinoma, and it may have become more frequent since the discovery of x rays, but it was quite common before x rays were known, and it is a natural evolution of the disease process known as lupus. By the examination of sections at and just outside the growing edge of areas of non-ulcerative lupus, I have been able to show* that the disease is essentially an obliterative tuberculous lymphangitis which destroys the lymphatics (Figs. 7 and 8). The characteristic lupus nodules found in the dermis are produced by proliferation of the endothelium of the affected lymphatics. The earliest stage of the lymphangitis is seen in apparently normal skin outside the visible edge of the diseased area (Fig. 7); and here also papillary hypertrophy of the diseased papillae can be seen. Passing back to the centre of the area of lupus, progressive enlargement of the papillae up to five times their normal length can be seen. Here, then, it is evident that blocking of the lymphatic is the primary factor, with chronic papillary hypertrophy as its consequence. The further development of the papillary areas into carcinoma is a matter of common clinical knowledge. If tubercle affecting the skin may cause papillary hypertrophy, may produce definite papillomata, and may ultimately give rise to cancer, it would seem likely that tubercle in other parts of the body may have the same result. It is perhaps significant that the form of lupus which most commonly produces cancer is the non-ulcerative or papillary form in which there is lymphatic obstruction without ulceration or destruction of tissue. This fact lends colour to my suggestion that multiple papillomatosis

of the large intestine, and also papillomata of the bladder, are really products of abortive local tuberculous infection occurring in early life.

In this connexion I would draw your attention to some very interesting observations by Dr. Thomas Cherry⁷ of Melbourne. He ascertained statistically that whereas during the last thirty years the death rate from tuberculosis has greatly diminished and that from cancer has greatly increased, the combined death rate from tubercle and cancer together has remained at a constant level. This curious fact, though susceptible of several interpretations, in his opinion indicates that persons who recover from an attack of tubercle are likely in later life, and as a consequence of their attack of tubercle, to die of cancer. Since every tuberculous infection is of the nature of a chronic lymphangitis, and must leave behind it some degree of lymphatic obstruction, Dr. Cherry's facts, derived from the whole mortality experience of England over a long series of years, offer rather a startling suggestion of the importance of tubercle, and hence of lymphatic obstruction, in the etiology of cancer. Early this year Dr. Cherry published in the *Medical Journal of Australia* a paper in which he records that, by the subcuticular injection of active tubercle bacilli in mice, he has been able to raise the incidence of malignant tumours to a significant extent in the mice experimented on. These experiments call for repetition and confirmation. It is certain that under modern conditions an abortive attack of tubercle is a common event of early life. The frequency of healed scars at the pulmonary apices and of tuberculous tonsils and adenoids suffices to prove this. May not mild, undetected tuberculous infection of the mammary glands in childhood leave behind it areas of lymph-stasis which give rise in middle life to duct papillomata and carcinoma of the breast?

Where I would differ from Dr. Cherry is in denying to the tubercle bacillus any specific role in the production of cancer. In my opinion any pathological process which

gives rise to lymphatic obstruction may be a cause of cancer. The specific factor is not the particular organism concerned, but the lymphatic obstruction to which that organism may give rise.

The tubercle bacillus is not the only organism which finds itself at home in the sluggish stream and quiet backwaters of the lymphatic vessels. The history of syphilis is mainly a study in the pathology of chronic lymphangitis. The primary lesion is

FIG. 16.—Gummatous elephantiasis of the right leg. From a case seen with the late Dr. J. J. Pringle.

a local proliferative lymphangitis. There follows enlargement of the regional lymph glands, and then an invasion of the great fascial lymphatic plexus with an accompanying secondary rash, often presenting papillary lesions. The mucous membrane where it joins the skin is next invaded, and here lymphatic obstruction is clearly evidenced by the appearance of condylomata, mucous patches, and moist papillomata of the tongue and lips. Then, in the tertiary stage, the deeper lymphatics are invaded, and gummata, which are areas of local proliferative lymphangitis, make their appearance (Fig. 16). The chronic glossitis which syphilis leaves behind it is an obstructive lymphangitis, known frequently to lead to papillary hypertrophy and carcinoma. Carcinoma of the lip and of the inside of the cheek frequently arises on the scar of an old mucous tubercle.

Chronic lymphangitis is not exclusively caused by the organisms of tubercle and syphilis. It may be due to many other organisms—for instance, to the members of the pyogenic group—and these organisms, also, in so far as they may produce lymphatic obstruction, are potential cancer-producing agents. Chronic lymphangitis may also be set up by a chemical or thermal agency. I have already given *prima facie* reasons for thinking that tar cancer, and the kangri cancer of Kashmir, and the epithelioma which occurs on the scars of old burns, are caused in this way. The fact that spontaneous tar cancer in man is usually preceded for years by the appearance of crops of warts which drop off, leaving a pigmented area, is presumptive evidence of the coexistence of a chronic lymphangitis, and the initial lesion of the tar carcinoma of mice is usually a papilloma.

Papillary hypertrophy as a consequence of pure lymphatic obstruction, apart from local infection, is perhaps best seen in elephantiasis. I have also produced it experimentally in the ear of the rabbit by placing an elastic ligature, not so tightly as to strangle the blood vessels, round the base of the ear. Warts not rarely occur upon prolapsed rectal mucosa, and may become malignant (Fig. 17).

FIG. 17.—Prolapse of rectum with polypi.

Is there any connexion between elephantiasis and carcinoma? If my contentions are correct, there ought to be. Well, I would point out that the chronic ulcers of the legs so often seen in elephantiasis may become malignant. A more striking example of the connexion is within my experience. A lady who had lived in India for many years came home with typical elephantiasis of one leg. She was persuaded by a friend's advice to try radiant heat baths for the leg, and shortly afterwards virulent multiple epitheliomata, twenty or thirty in number, appeared on the skin of the affected leg. The regional glands became enlarged and she died in a few months.

In this case, judging by the multiplicity and activity of the growths, the cancerogenous factors were very active. The diseased leg differed from the healthy one in two obvious respects: it was the seat of long-standing lymphatic obstruction, and its surface when in this condition had been subjected to irritation by heat and light.

In this address I have dealt with a great subject, and necessarily, in the present state of knowledge, my remarks contain a large element of speculation, though for the sake of brevity and emphasis I have put them in dogmatic form. I shall be content if you admit my proofs that lymph-stasis lies at the root of cancer—certainly of carcinoma, possibly of sarcoma. For the rest, my address is a working hypothesis, which may perhaps serve to orientate the work of younger men.

The anatomist, the physiologist, and the biochemist, and I would add the physician, have devoted too little attention to the lymphatic system. The biologist has never attempted to produce from a unicellular organism a bicellular one, still less a multicellular one. There exists, I believe, a four-celled organism, two of whose cells only possess mouths. Here in embryo is the multicellular animal. I challenge the biologists to produce experimentally a two- or four-celled organism from a unicellular one. When this has been accomplished, the converse problem, that of the origin of cancer, may prove easy of solution.

In conclusion, I do not want a tombstone, but neither am I content to lie under the green turf of oblivion: I would like to be remembered for two things: first, as having shown twenty-five years ago that cancer spreads mainly by lymphatic permeation; and secondly, as having demonstrated to-day the importance of lymph-stasis in its etiology.

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