MECHANICAL IRRITATION AS ETIOLOGIC FACTOR OF CANCER *

CLINICAL OBSERVATION

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Virchow's[1] "Irritation Theory," promulgated in 1855, has remained the most plausible and fruitful hypothesis for the etiology of neoplasms. This theory states briefly that: "Irritation is the essential factor of neoplastic tissue proliferation." His general principles concerning neoplasms, concisely formulated as "*omnis cellula e cellula*" and many other of his principles have stimulated the study of tumors by persistent empirical-clinical observations and were largely responsible for the numerous other theories explaining the origin of tumors (Cohnheim, Ribbert, etc.). These clinical and morphological studies, in turn, have led to extensive and systematic experimental work which in the hands of such investigators as Fibiger, Rhodenburg, Yamagiwa, Ichikawa, Bloch and others, of recent years, has brought out startling and convincing evidence in favor of the theory.

One of the earliest general principles laid down by Virchow declares that "For the production of vital activity of any part of the body, excitation or, in other words, irritation is necessary." Applying this principle to the formation of neoplasms, he made the deduction that "The production of large groups of cells from single ones occurs in the adult body unquestionably as the result of direct irritation of the tissues."

By means of analysis of a rich collection of empirical observations and experimental data, Virchow developed further details of the irritation theory. He recognized numerous single factors, as for example: "In case of mechanical irritation caused by a thread, the swelling is due to division of cells." "If the skin becomes irritated in consequence of continued friction and the irritation is increased to a certain point, the epithelium will thicken and, if the proliferation is very energetic, it may lead to tolerably large tumor-like

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formations." "The same effect, cell proliferation through cell division, may also be produced by chemical irritation as by the application of a caustic substance." As definite clinical examples of such irritations, Virchow referred to lip cancers of pipe smokers, and to cancer of chimney sweepers. It was through the study of the latter that the importance of tar as a chemical irritant has been demonstrated, and that the isolation of a chemical compound from tar by Bloch led to the production of cancer in animals almost at will.

Besides the action of chemical, mechanical and thermic irritants (*causa occasionalis*), emphasis is laid upon the importance of the local reaction of tissues with subsequent thorough and complex changes comparable to those occurring in the fertilization of the ovum after the action of the spermatocyte. This tissue reaction forms the second important factor in tumor formation, the *causa praedisponens*. In a long series of diverse conditions of local pre-disposition, Virchow emphasized the importance of *locus minoris resistantiae;* for instance, where derivatives of ectoderm and entoderm meet (orifices of the body, lip, anus, etc.), or in the viscera, the narrowed places (flexures, etc.) of the intestines which, because of their positions, are more exposed to irritation. The hereditary element of the local predisposition, is demonstrated in the congenital naevi (*n. verrucosus*, *n. pigmentosus*, etc.). On the other hand, as examples of acquired predisposition, Virchow [2] brings up a series of post-inflammatory changes: scars, polypi, etc., and emphasizes mainly the general fibrosis following chronic inflammation. The mucous membranes deserve mention particularly on account of the frequent hyperplasia, incited by the chronic inflammatory irritation, which in turn may often lead to real tumor formation (polypi).

The third important factor in production of neoplasms is the general *dyscrasia*, which however has to be strictly distinguished from *constitutional disposition*. This latter involves the changes of the tissue juices and blood as well as the alteration of all the body tissues proper. On the other hand, *dyscrasia* according to Virchow is always secondary to some local tissue changes. The essential changes of *old age* he found in various tissues. These are followed secondarily by *dyscrasia*. Various single factors usually combine in the production of tumors; for instance such is the case when an undescended testicle (developmental defect) is exposed to trauma, a

combination of local misplacement and mechanical irritation. The various irritants, as single factors, usually combine for the production of neoplasms; according to Virchow, "inflammation never admits of a single explanation; we can find side by side all the forms of irritation."

This tumor theory opened a wide experimental field for cancer research which however has only recently made rapid progress. For such work accurate clinical and morphological observations form a firm working basis. The purpose of this paper is to record a singularly interesting clinical observation in which the mechanical factor seems to be predominant in the production of cancer. The subsidiary factors must necessarily play a significant rôle, but the degree of their importance is obscure.

Case Report

Patient W. L. K., male, 60 years old, white, was admitted to the service of Dr. K. I. Sanes in the Western Pennsylvania Hospital, Pittsburgh, Pa., on Aug. 15, 1915, with the chief complaints of (1) abdominal pain, (2) constipation, (3) loss of weight, (4) anorexia.

Family History. Mother strikingly emaciated, died of old age.

Past History. Negative.

Present Illness. Began about one year before admission to the hospital with obstinate constipation. Six months later patient began to suffer from severe abdominal pain, which was pelvic in site and which often awakened the patient from his sleep. Later these attacks of pain with the same localization occurred during or immediately after meals. About two weeks before admission to the hospital patient had very severe attacks of griping pain of the same type as mentioned before, with nausea but without vomiting. His constipation became very bad and patient began gradually to develop obstructive symptoms. He lost 36 pounds in weight within the past six months (from 171 to 136 pounds).

Physical examination of the abdominal cavity revealed a moveable hard mass, probably of the sigmoid. Blood count was negative. Urine contained some acetone. Stool examination showed the presence of blood. Roentgenologic examination showed complete obstruction of the sigmoid somewhat below the end of the descending colon. Bismuth meal did not pass into the sigmoid. The bismuth column showed the same position at the end of thirty-eight hours. The bismuth enema passed this place although it did not fill up the descending colon.

Clinical Diagnosis. Carcinoma of the sigmoid.

Operation of sigmoidectomy was performed by Dr. K. I. Sanes at the Western Pennsylvania Hospital on August 19, 1915. A hard, constricting growth of the sigmoid was found below the junction with the descending colon. The growth had not invaded the serosa which had a smooth surface, but with some cicatrization of the meso-colon involving the inferior mesenteric artery. About 12 inches of the large intestine were resected with electric cautery. The growth occupied about the middle of the removal bowel. The operation was compli-

cated by interference with the blood supply of the lower bowel. The inferior mesenteric artery had to be ligated, as it was involved in the above-mentioned cicatrix. Consequently the descending colon was removed for the most part and the remnants of the colon and the sigmoid were united in an end to end anastomosis. The abdominal cavity showed nothing unusual otherwise. The liver was slightly enlarged, but no hard nodules were discernible in it.

The patient's convalescence was uninterrupted and after complete recovery he was discharged from the hospital on September 13, 1915. The last roentgenologic examination, in March, 1922, revealed the formation of a slight diverticulum at the place of the anastomosis. The patient, however, had made no complaints; his bowel movements and digestion have given him no trouble and he is still enjoying good health at present.

Pathologic Report

Gross Examination. Specimen consists of a piece of large intestine 30 cm. in length (Fig. 1). At about its middle portion a circular constriction is seen, which is hard in consistence and is covered with scar-like depressions and fibrous tags, but nothing else is noticed on the outside. Above the constriction the bowel is obviously distended, its wall is leathery and thickened as compared with the portion below the constriction. On opening, the knife meets with increased resistance when cutting through the constriction. The lumen shows a striking picture. There is an annular, ring-formed elevation constricting the lumen. It measures 4.5 cm. in width and averages 2.5 cm. in thickness. On cut surface a gray growth is seen with bacon-like, transparent appearance which shows gradual transition at its base to tendinous fibrous tissue, and at its periphery to yellow, subserous fatty, material. This ring-formed constriction has rather sharp, elevated edges and a depressed, crater-like middle portion. The surface of the crater is covered with hemorrhagic and necrotic material. The lumen here measures about 1.5 cm. in diameter and is filled completely by a round polyp. This has a mulberry surface covered with mucus and is soft in consistence. It forms the head of a long pedunculated growth with a broad attachment 8 cm. above. The stem is fan-shaped at its attachment (8 mm. at its base) and tapers to a neck where it measures 3 mm. in thickness. The round head of the polyp has a valve-like action and can be dislodged from below. It fits in snugly in the crater-like center of the annular growth, as a ball in a socket. On cross section, the head of the polyp shows soft consistence and rich mucoid secretion of the surface layer. A peach stone is lodged above the entrance of the constriction and

presses against the polyp. The stone is slightly larger than the lumen at the constriction and has otherwise the usual, rather rough surface and edges.

Above the constriction the mucosa is somewhat thickened and covered with mucus. The musculature shows obvious hypertrophy. The muscle layer measures 4 mm. in places. On one side there is a peculiar, rather superficial pouch lined with mucosa as elsewhere but with strongly developed musculature. The pouch seems to have been the nest for the peach stone.

Microscopic Examination. Section taken from the annular constriction at the crater-like ulceration shows a malignant epithelial growth. The glandular structure of the growth is well preserved in most places. The transition from the normal epithelial covering to the irregular epithelial proliferation can be followed distinctly (Fig. 2). The malignant cells vary a great deal in size and shape. In the glandular portions they are rather cylindrical with irregularly placed nuclei which show numerous mitotic figures. In the scirrhous portion, the cells are quite small. In the central portions the surface is necrotic. In the deeper layers the cells are smaller and surrounded by large amounts of dense fibrous tissue. This scirrhous growth, however, has not invaded the subserous tissues. The stroma increases in amount towards the deeper layers and contains a marked infiltration of lymphocytes. Section of the head of the polyp shows a benign epithelial tumor (Fig. 3). The surface shows typical intestinal glands, mostly perpendicular to the surface. In the deeper layers the glands run an irregular course and consequently they are cut in various planes. The cells are very regular in every respect. They are cylindrical with nuclei placed near the basal membrane. The blood vessels are well formed. Around the hilum they have also a muscular wall and are surrounded by fibrous stroma which contains scant lymphocytic infiltration. The surface epithelium consists mainly of goblet cells with increased mucus secretion which also covers the surface of the growth. Sections of the stem and base of the polyp show dense fibrosis and rich lymphocytic reaction. There are quite a few eosinophilic leukocytes present. Some sections of the intestinal wall above the constriction show marked hyperplasia of the smooth muscle cells. Van Gieson's and Mallory's connective tissue stains reveal an increase of fibrous tissue with diffuse lymphocytic infiltration.

Anatomic Diagnoses. Scirrhous carcinoma of large intestine; pedunculated adenoma of large intestine; dilatation of intestine and muscular hypertrophy of intestinal wall above constriction.

Discussion

From the pathologic study of the specimen it is evident that we are dealing with a carcinoma of the sigmoid, which originated where the head of the polyp caused friction of long duration. Obstruction was brought about by the ball valve-like mechanism of the polyp and cancerous constriction. Above this there is a marked muscular hypertrophy of the intestinal wall. Primarily this hypertrophy was due to the effort of the intestine to expel the polyp. This effort of expulsion pulled out the polyp and produced an unusually long stem (8 cm.). Unquestionably a long time was necessary to accomplish this. Later on, when a constriction was brought about and thus prevented the progress of the peach stone, the attempt to expel the stone produced an additional muscular hypertrophy by the same mechanism, with the result of a pouch-like irregularity of the intestinal wall. These conditions seem to indicate a well-marked mechanism of long duration. The formation of the polyp was probably due to a previous chronic inflammatory process. There is strong evidence for the causative relation between the head of the polyp and the cancerous growth, which corresponds accurately to each other as to location where the friction occurred, as a ball in a socket. This is particularly striking in view of the long stem. All of this seems to exclude a mere coincidence. The peristalsis of the intestines produced the continuous to-and-fro friction which had been increased by the effort of the intestines to expel the polyp and the peach stone. The head of the polyp, perhaps, did not remain in the place of constriction for a long period. This may explain the clinical observation that the patient never had complete obstruction. Still another factor of mechanical irritation may be added in the nature of fecal concretions which seem to play an important rôle in the production of cancer at the various flexures of the large intestine.

There are numerous empirical observations as to neoplasm caused by chronic mechanical irritation. Bashford[3] reported cases of melanosarcoma occurring in natives of Africa, which are caused by thorns causing continuous irritation of the sole of the foot. Cancers caused

by irritating foreign bodies (pessaries, etc.) have often been reported. Very striking also is the "cancer of the horn core" of Indian cattle, which develops at the root of the right horn used for attachment of agricultural implements. No cancer develops on the left horn of these cattle. Stones in gallbladder and renal pelvis as well as cancers of the tongue, which correspond to bad teeth and lip cancers of pipe smokers, have an inflammatory element in etiology besides the pure mechanical irritation. In the case reported in this paper, both the cancer and the polyp have the inflammatory factor in their etiology. This is unquestionably of primary importance particularly as far as the formation of the polyp is concerned. The proof of this is seen in diffuse fibrosis and lymphocytic infiltration at the base of the polyp. Post-inflammatory fibrosis has been recently emphasized in the so-called precancerous-lesions. The older and ancient authors used the term of "scirrhous induration" not only for cancers, but also for inflammatory fibrotic lesions. Galen[4] stated that *polypi aut inflammatione aut tuberculo*. . . . Galen emphasized the importance of inflammatory lesions and "other nodules" preceding the formation of cancers besides the general dyscrasia, *atra bilis*.

This has been given a strange, literal interpretation, whereas it represents the humoral pathologic conception of Hippocrates and Galen. It has been accepted also by Virchow, although he considered the humoral changes secondary to the tissue changes as seen in old age. Local cancerous predisposition of the sigmoid can be assumed on an embryological basis, also shown by the peculiar development of the mesosigmoid as contrasted with the mesocolon above and below it.

Conclusions

1. The case of carcinoma of intestine reported in this paper appears to present a striking example of mechanical irritation as an etiological factor in the histogenesis of cancer.

2. The case is analyzed and best understood by means of Virchow's "Irritation theory." According to this any of the single factors of three groups may be predominant in the histogenesis of cancer, which, however, is usually the result of various combinations of them.

These groups are, (*a*) *Causa occasionalis*, as the various irritants: mechanical, chemical, or thermic.

(*b*) *Causa predisponens*, as the embryological anlage or post-inflammatory changes.

(*c*) *Dyscrasia*, as general constitutional change.

The various well-known cancer theories and recent experimental works (Conheim's, Ribbert's tar cancers, etc.) represent only emphasis and elaboration of single factors in Virchow's comprehensive theory.

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2. R. Virchow. Die Krankhaften Geschwülste. Berlin, 1863. 36. 64. 375.
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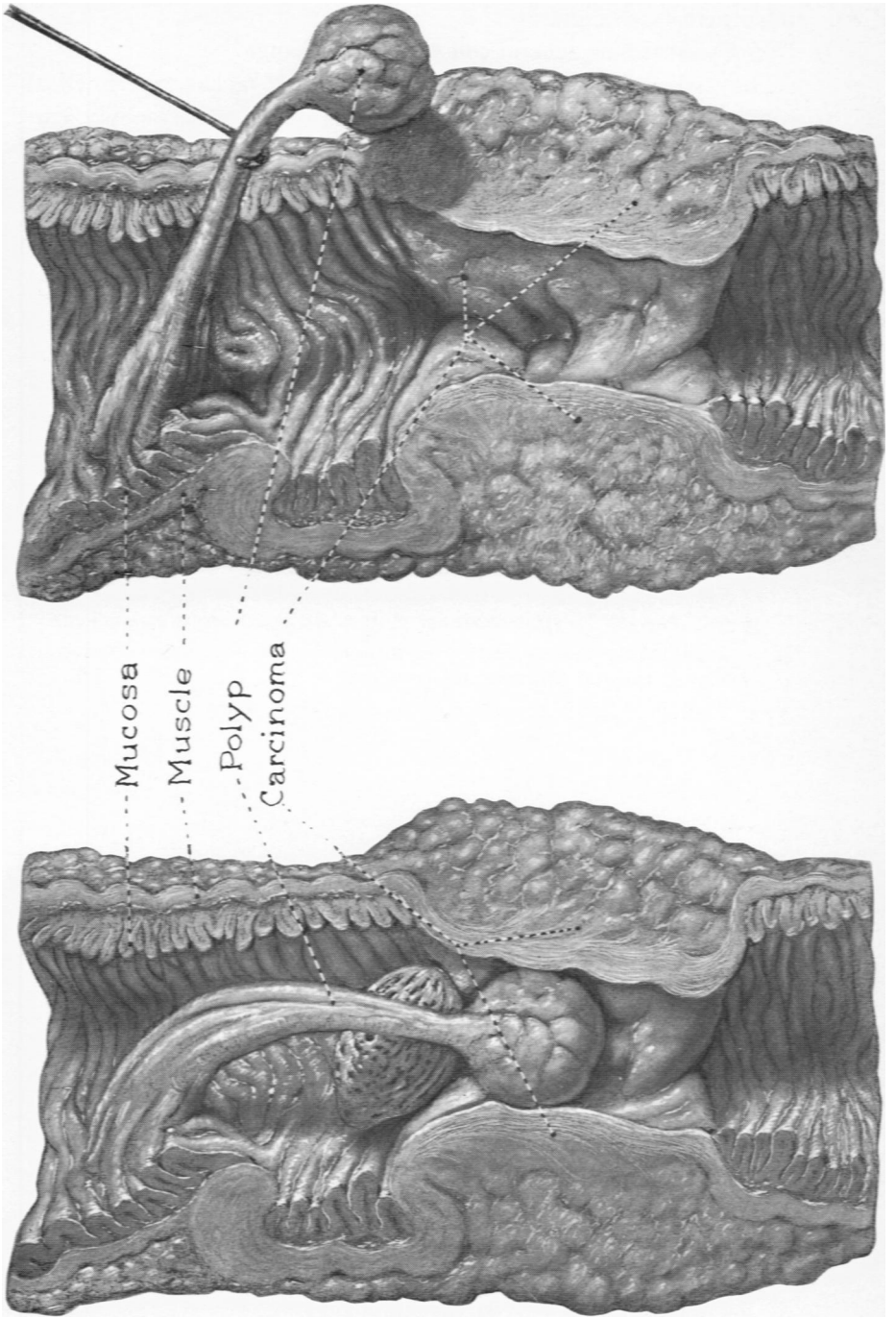
4. Galeni. Pergameni Omnia. Ex Editione. Frobenianae, 1612.

DESCRIPTION OF PLATES LXXXVII–LXXXVIII

Fig. 1. Drawing of specimen, showing lumen of intestine. *At left:* Annular constriction of scirrhous carcinoma. Lumen is completely plugged by head of polyp with long stem (ball in socket). Above head of polyp is the peach stone. *At right:* Polyp is lifted out of its nest. Peach stone is removed.

Fig. 2. Photomicrograph of section of intestinal wall, showing transition of normal epithelium to malignant proliferation. X 35.

Fig. 3. Photomicrograph of section of head of polyp, showing intestinal adenoma. X 35.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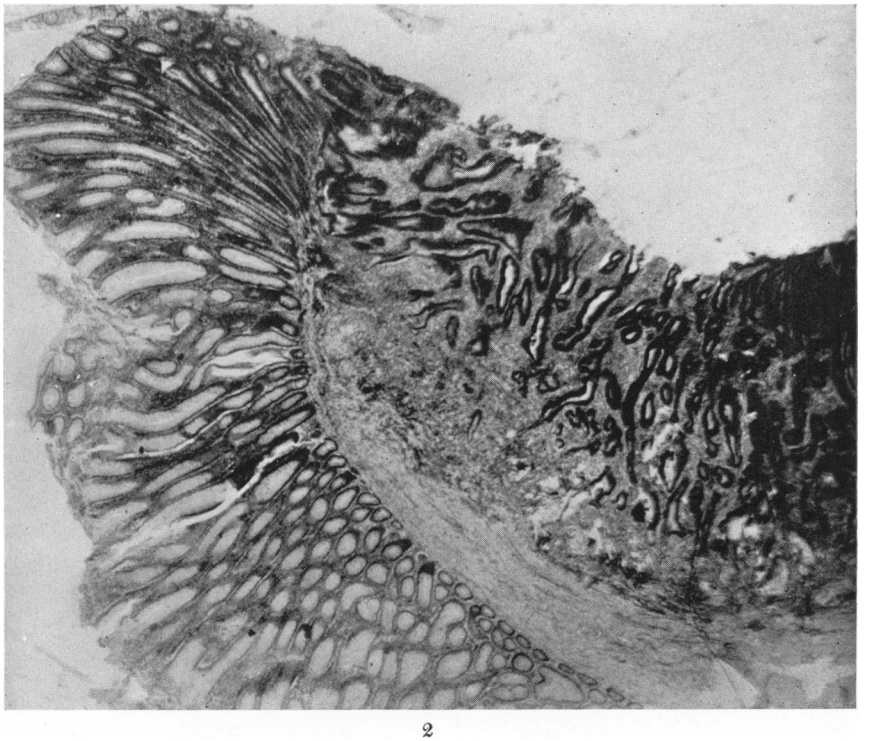

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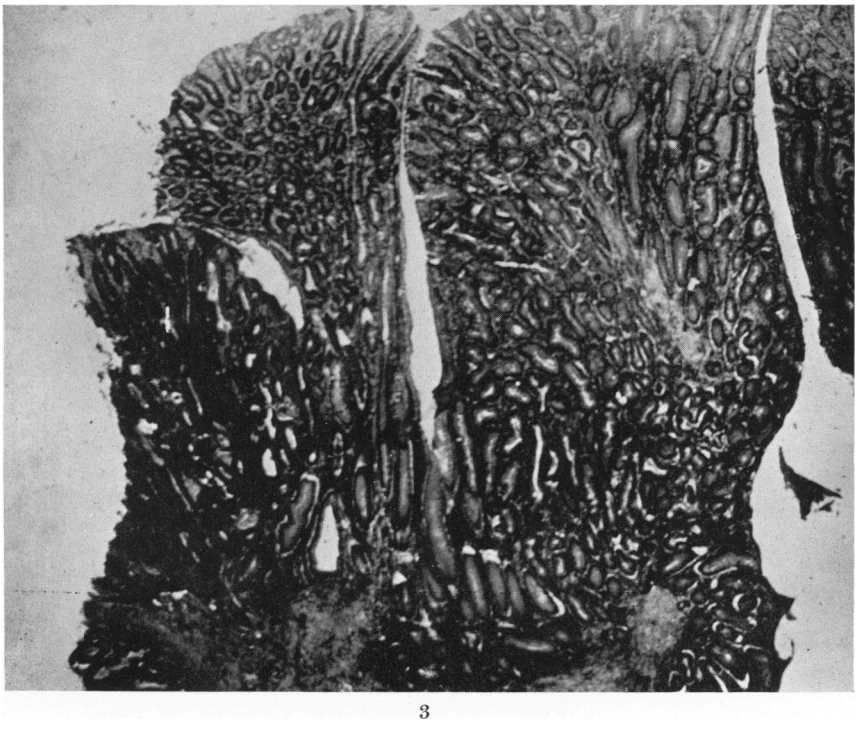

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