A REMARKABLE CASE OF CARCINOMA OF THE GALL-BLADDER IN A MAN TWENTY-TWO YEARS OLD.

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The occurrence of carcinoma in individuals between the ages of 15 and 30 years has been positively established by observations within the last two decades. I shall not speak of congenital carcinoma or that occurring in early childhood.

The statistics of Bürger founded on 15,134 autopsies, give 39 cases (25 per cent.) of carcinoma in persons between the ages of 15 and 30 years. None under 15 years are given. De la Camp, in 9,926 cases of carcinoma, found that the patients in 19 or 0.18 per cent. were under 20 years of age. Lubarsch, in 563 cases, found 4 patients between the ages of 14 and 19; 5 between 20 and 25 years and 3 between 26 and 29. Of 527 autopsies on carcinoma cases by Glaser one subject was 20 years of age and 16 were 30 years of age. Of 325 autopsies on carcinoma cases recorded by Borst one subject was between 11 and 20 years and 2 were between 21 and 30 (.92 per cent.). The percentage therefore varies within wide limits between 0.18 per cent. (De la Camp) and 3.22 per cent (Glaser). The average in the 5 series of statistics is 0.87 per cent. Of all cases of carcinoma reported but 1 per cent. appeared before the age of 30.

The organs most frequently affected in young individuals are: The rectum between the thirteenth and the twenty-fifth years and in some cases even earlier—(Billroth, Bürger, De la Camp, Gurlt, Glaser, Czerny, Port, Sehöning). The stomach is seldom affected before the thirtieth year, but De la Camp, Hofmann, Muth and Borst have recorded cases at the ages of 14, 16, 18, 20, respectively. Ovaries have been found affected at the ages of 17, 19 up to 30 years (Bürger, Malibert, De la Camp, Leopold). The uterus not infrequently between 20 and 30 and in exceptional cases (Bürger, Eckardt, Glaser, Beigel) as early as 17, 19 and 20 and up to 30 years. Further, cancer of the vagina has been found as early as the fifteenth year (Brückner, Küstner) and up to the twentieth and thirtieth year. The skin has been affected at the ages of 23 to 27 (Pierre, Andouard). The appendix at 17, 19, 24, 30 (Kelly, McBurney, Adam).

I report a case of carcinoma of the gall-bladder in a man of 22 years, to my knowledge the first case recorded at so early an age, the youngest patient previously reported (Kaufmann) being a woman, aged 35, in whom gallstones were also present. The case I now report is especially interesting for three reasons: 1. The individual was a male. In men carcinoma of the gall-bladder is much rarer than in women.¹ 2. From the etiologic standpoint, no gallstones, which are supposed to play an important part in the formation of carcinoma of the gall-bladder, were found. 3. From the clinical standpoint, a relatively benign course of the disease.

Many authors (Bollinger, Marchand, Klebs, Zenker, Musser, Fütterer) look on gallstones as a primary cause of carcinoma of the gall-bladder; 79.7 per cent. of 74

cases recorded by Tiedemann showed an existence of gallstones. Janowski found stones in all 40 cases which had come under his observation. Siegert found gallstones in 31 cases of 39 and Fütterer found same condition in 78 per cent. of 268 cases.

Patient.—A. D., Italian, laborer, aged 22, was admitted to Mercy Hospital, May 13, 1906.

History.—Patient had typhoid fever 10 years ago. For past 3 months patient has had indigestion and pain in epigastrium. Pain lasted three to four hours, then passed away. Bowels were constipated. Patient was jaundiced.

Examination.—Patient was fairly well nourished. Temperature was normal; pulse, 90, regular and good volume; respiration, 20. Tongue was coated. Sclera was slightly yellow. Heart and lungs were negative.

Abdomen: There was a mass in epigastrium size of orange, slightly to right of the median line. Mass moved with liver and respiration. There was tenderness over mass.

Clinical diagnosis: Cholecystitis.

Operation.—By Dr. Acheson Stewart. Incision was made in the median line. Gall-bladder the size of an orange was found, adherent to abdominal wall. The gall-bladder was very friable and its cavity filled with pus. Mass was dissected free as far as possible, ascendently fixed, partially excised and remainder packed; two pieces of gauze were used, one in the gall-bladder, the other in the abdominal cavity. Convalescence was uneventful. Patient was discharged June 7, 1906. Small granular surface at incision.

Examination of Tissue Excised.—Gross appearance. This consisted of a section of tissue the size of a walnut, grayish-white in color, of semi-solid consistency infiltrated by yellowish striated, isolated small round and oblong masses.

Microscopic Examination: Under weak power: The gall-bladder wall consisted mainly of connective tissue with some non-striated muscle fibers. Throughout the field were infiltrations of small round carcinoma cells which in some places were massed in groups, in other places diffused, the latter areas very vascular, containing leucocytes, lymphocytes, and many fibroblasts. Where the carcinomatous infiltration was great the connective tissue had undergone hyaline degeneration, some places still responding to stains, others appearing clear and transparent, with no affinity for stains.

Under high power: The carcinoma cells were more or less uniform in size with roundish or oblong, strongly chromatinized nuclei, surrounded by a narrow mass of protoplasm. The protoplasm was of absolutely homogeneous structure, in some places finely granular and weakly basic. Mitosis was shown but very little. In the center of the carcinoma cell masses are found all kinds of katabiotic changes, karyolytic degeneration of chromatin, etc. In many places the carcinoma cells had undergone colloid degeneration, the protoplasm was swollen, nucleus flat and periphery compressed. (Fig. 1.) In the beginning of colloid degeneration the protoplasm of the carcinoma cells took weak (acid) anilin dyes; with further degeneration this property was lost. The degenerated cells had run together and formed round light areas (Fig. 2), producing a honeycomb appearance, giving the impression that the cancer cells had been lost. The frame of the honeycomb consisted of a hyaline branching mass in which the flat nuclei of the degenerated cells were deposited. That the carcinoma had undergone colloid degeneration was shown by the fact that some of the alveoli were still filled with perfect carcinoma cells. Where the carcinoma cells were diffused the connective tissue also presented a homogeneous mass of colloid degeneration which was partially absorbed and partially (shown under freezing) fatty degenerated. (Fig. 3.) Whether it was fatty infiltration or degeneration could not be positively ascertained; most likely it was infiltration. Differential diagnosis lay between carcinoma, sarcoma, granulation tissue, specific (tuberculosis, syphilis) or simple. Under weak power it first appeared to be a round-celled sarcoma, in some places diffusely infiltrated, in others the alveolar variety. Under stronger power and stained according to Van Gieson as modified by Mallory an intercellular substance between the carcinoma cells could not be demonstrated. Also in the diffused places the carcinoma cells were arranged in longitudinal

1. According to Dr. Bollinger, the ratio is 80 women to 20 men. In 99 cases of primary gall-bladder cancer 85 were women and 14 men (Siegert). Tiedemann recorded 88.7 per cent. women and 11.3 per cent. men. On account of lacking, women suffer much oftener than men. Bollinger found corset livers in 33 per cent. to 40 per cent. of gallstone cases.

strata between the connective tissue. The Van Gieson stain showed the absence of intercellular substance. The absence of the finely (threadlike) or finely granular intercellular substance was the most important differential point between sarcoma and carcinoma. The morphology was also different. The spheroidal carcinoma cells on cross section were of uniform size, while the cells of sarcoma appear of various sizes and shapes on cross section. Still less could it be taken for plastic granulation tissue which is traversed by rich capillaries and contains embryonic connective tissue cells (fibroblasts), leucocytes and lymphocytes. The tumor in some places had such an appearance, but the carcinomatous areas were sharply defined from the granulation tissue. Tuberculosis and syphilis were ex-

Fig. 1.—Section through the thickened gall-bladder wall (lower power, Zeiss objective 16 mm., ocular 4). Showing the infiltration with carcinoma cells and colloid degeneration.

cluded as the tubercle bacilli and spirochetes were not found. The above carcinoma may be designated carcinoma globocellulare colloides (or endothelio-carcinoma?).

Probably the carcinoma originated in the lining epithelium of the gall-bladder. This cannot be positively ascertained since the specimen excised had no mucous

Fig. 2.—Section through the thickened gall-bladder wall (higher power, Zeiss objective 8 mm., ocular 4). Showing the middle carcinoma cell-nest in the center beginning necrobiosis of the carcinoma cells.

membrane. It is possible that the primary seat was in the endothelium of the lymph vessels. The above variety is seldom found in the gall bladder, more generally we find adenocarcinoma, then scirrhus and medullary forms. Squamous epithelioma occurs very seldom (metaplasia of mucous membrane from columnar to squamous epithelium takes place).

A remarkable feature was the small morphologically

indifferent structure of the carcinoma cells. I shall also report a case of carcinoma of the appendix in a man, aged 30. Microscopically it is identical with the specimen from the gall bladder.

It is possible that the exciting cause of the carcinoma was the cholecystitis, moreover, that pus was found in the gall-bladder. The inflammation is presumably not to be considered the direct cause of carcinomatous degeneration but it is more likely to be attributed to secondary causes.

The parasitic origin can be absolutely excluded as all most painstaking thin paraffin preparations and staining methods gave negative results. Another interesting feature was that at the operation metastasis could not be found, even the portal lymph glands were not enlarged. We deal, therefore, with a purely local carcinoma which clinically and microscopically gave no evidence of metastasis. It can be likened to skin carcinoma which affects distinct areas without tendency to metastasis.

From a pathologic standpoint the benign course of this carcinoma is very important because it shows that cancer is primarily a local affection and may remain so for some time. Why metastasis should be absent in these cases is so far a question, the answer to which may

Fig. 3.—Diffuse colloid degeneration with some well-preserved carcinoma cells (higher power, Zeiss objective 8 mm., ocular 4).

aid greatly the therapy of carcinoma. Theoretically, it may be assumed that the organism becomes immune to metastasis either through histogenic or serogenic influences; if the latter, the carcinoma cells become destroyed cytolytically in the blood serum or, which is the most likely, the fixed cells and not the blood stream insure the immunity against secondary metastasis.

Postoperative observation for several weeks shows that although the greater part of the diseased gall-bladder was left in the abdomen there is no tendency to metastasis. The patient feels well physically and is gaining in weight. The periodical pains experienced prior to operation are gone.

In conclusion a question arises whether the carcinoma became stationary and is capable of healing. Theoretically, according to Virchow, the spontaneous healing of cancer is not improbable. Within the last few years cases have been reported in which positive diagnosis of carcinoma was established microscopically and in which, inspite of incomplete removal of same, recovery took place. I refer to cases of A. Senger²

2. "Ueber die spontane Heilbarkeit des Carcinoms," Chirurgen-Kongress, 1894-1903, No. 12.

and H. Mohr.³ Both speak of healed carcinoma of the buccal mucous membrane. Furthermore, Alsborg, Kroenlein, Steudel, Lindner, Hahn and Baer reported cases of stomach carcinoma in which after a simple gastroenterostomy was performed the tumor subsided and in some cases completely disappeared. Nusbaum suggested that the relief of hyperemia and removal of irritation not only acts as a prophylactic agent, but may also retard the development of carcinoma. It is possible that my case may belong to this class. Through the emptying of the gall-bladder of the inflammatory products and irritation and hyperemia

Fig. 4.—Section through the shrunken remaining gall bladder, hyaline sclerotic degeneration of the fibrous and muscular tissue (lower power, Zeiss objective 16 mm., ocular 4).

being removed, recovery is not improbable. I hope to keep the patient under observation and report again the further course of the disease.

Additional Notes.—Since writing the above further observations on patient have been made. On August 19, about 13 weeks after the first operation, the patient presented himself at the hospital. He had felt perfectly well during the entire

Fig. 5.—Section through the fibrous capsule of the remaining gall bladder, showing well-preserved carcinoma cell-nests with beginning necrobiotic changes of the cells (higher power, Zeiss objective 18 mm., ocular 4).

period since his discharge. A small fistula still remained at the site of incision, and through this, by means of a probe, a gall-stone could be felt. A second operation was decided on.

Operation.—By Dr. A. Stewart. Incision was made parallel to scar. On opening the abdominal cavity the gall-bladder was found very much shrunken, from the size of an orange to a mass 5 c.m. long and half the thickness of a finger. The distal end was adherent to the peritoneum and contained in its small

cavity a cholesterol stone about the size of a pea. The stone was very likely formed after the first operation from the incrustations of dead epithelium and cholesterol. The gall-bladder was tied off, extirpated and the abdomen closed. A careful palpation of the liver as well as of the peritoneal cavity showed no metastasis.

The remains of the gall-bladder are of fibrous consistency and the superficial covering very red. On cross section two distinct tissues are recognized; a grayish-white oval mass about one and one-half centimeters in diameter with a very small lumen in its center and surrounded by a tough fibrous capsule.

Microscopic Appearance.—(Eosin hematoxylin stains). The gray oval mass (Fig. 4) consists of hyaline sclerotic connective tissue, pure in nuclei, and remnants of a few smooth muscular fibers. In the center is the lumen which is lined with a flat endothelium (remnant of the gall-bladder cavity). Under high power there can be seen in the hyaline sclerotic masses multitudes of necrobiotic carcinomatous cells. In some cells a part of the nucleus is still visible; the majority lack that and present only a light blue stained mass on the diffuse red underground. In the fibrous capsule, which is very vascular, the found roundish oval nests (Fig. 5) filled with carcinoma cells; the latter are in the majority nearly normal and of a dark blue color. On the other hand, there are also found in the center as well as periphery of the nest necrobiotic carcinoma cells. The nucleus is swollen and its staining property is almost lost; the protoplasm is broadened and stained a weak reddish blue. Fibroblasts are seen in large quantities, compressing and drawing together the nests.

The supposition that the removal of the inflammatory irritation may bring about the healing of carcinoma seems very probable. As is seen microscopically the gall-bladder shrank together and the carcinomatous masses underwent (with some exception) colloid degeneration; only in the outer fibrous capsule where the vascularization was so rich, were there still some carcinomatous nests, nourished and kept living; but even there the necrobiotic changes of the carcinoma cells have begun. They perish either through poor nourishment or the invasion of the fibroblasts which compress them.

It is logical to suppose that without extirpation the carcinoma would have degenerated and disappeared. We can therefore admit the interesting fact of the spontaneous healing of a carcinoma (which was positively diagnosed microscopically). This case shows that even in advanced cancer when the organism has sufficient fighting endurance recovery is still possible. At this time, however, we are not as yet capable of understanding the fine mechanism of this process in order to utilize it and to benefit the therapy of inoperable carcinoma.

EXPERIMENTAL CHRONIC NEPHRITIS.*

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From the slight mention which experimental work on chronic nephritis receives in our text-books and even in more exhaustive monographs on renal diseases it would seem that the result of experimentation conducted with the object in view of reproducing chronic Bright's disease and of elucidating some of the many obscure problems connected with it has been unsatisfactory. Ziegler¹ states very positively:

Die Experimentaluntersuchungen über Nephritis . . . lassen sich für die Pathologie der bei dem Menschen vorkommenden Nephritis nur in sehr beschränktem Maasse verwenden.

* From the Pathological Laboratory of Cooper Medical College.
1. Ziegler: Lehrbuch, eighth edition, 1895, p. 754.