

THE PREVENTION OF CARCINOMA OF THE GALL-BLADDER

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IN RECENT years, much attention has been directed towards the prevention of cancer by the education of the public concerning those various lesions which are generally considered to be precancerous. These efforts have, however, been concerned chiefly with cancer of the lip and mouth, the stomach, the breast, the rectum and the female genital organs. It is an astonishing fact that little or no emphasis has been placed upon the possibility of the prevention of cancer of the gall-bladder. In a paper presented by Doctor Ewing¹ himself, at the International Symposium on Cancer at Lake Mohonk, New York, in 1926, on "The Prevention of Cancer," nothing whatever was said about the possibility of the prevention of cancer of the gall-bladder. Moreover, I have not been able to find any article that has been published, at least in recent years, dealing particularly with the prevention, although, in occasional writings, attention has been directed to the frequency of carcinoma in this region.

It is difficult to understand why cancer of the gall-bladder has been neglected in all of the educational work that has been done by the American Society for the Control of Cancer and other similar organizations. It would seem that there could be only two reasons for this neglect: first, that it is considered to be a rare disease, and, second, that there would seem to be no way of preventing it. It is the purpose of the present paper to attempt to show that both of these ideas are erroneous.

The great frequency of carcinoma of the gall-bladder as compared with

| Name of authors | Buday | | Bejach | | Redlich | | Feilchenfeld | | Riechelmann | | von Berencsy and von Wolf | |
|--|-----------|-----------|-----------|-----------|-----------|-----------|--------------|-----------|-------------|-----------|---------------------------|-----------|
| | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| The number of autopsies from which the statistics have been compiled | 5,530 | | 6,808 | | 5,002 | | 5,022 | | | | 19,908 | |
| Number of cases of cancer | 336 | | 692 | | 496 | | 507 | | | | 2,314 | |
| | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. | Per cent. |
| Esophagus..... | 6.21 | | 20.3 | 0.8 | 17.3 | 2.8 | 21.3 | 1.6 | 20.0 | 1.4 | 11.88 | 0.61 |
| Stomach..... | 38.42 | 16.36 | 36.5 | 31.3 | 39.9 | 39.6 | 39.9 | 25.2 | 46.6 | 34.1 | 48.90 | 20.45 |
| Intestine..... | 5.64 | 1.05 | 8.2 | 6.1 | 4.2 | 6.1 | 4.3 | 4.3 | 3.7 | 3.9 | 5.34 | 2.75 |
| Gall-bladder..... | 1.12 | 2.10 | 1.9 | 8.5 | 3.5 | 10.8 | 1.2 | 9.1 | 3.9 | 9.5 | 2.77 | 10.18 |
| Breast..... | 0.56 | 5.80 | | 12.5 | 0.35 | 12.2 | | 12.6 | 0.3 | 8.3 | 0.09 | 6.85 |
| Ovary..... | | 14.78 | | 2.1 | | 5.1 | | 4.7 | | 4.0 | | 8.16 |
| Uterus and vagina | | 45.40 | | 13.3 | | 14.1 | | 17.7 | | 24.6 | | 35.99 |
| Uterus..... | | 44.35 | | | | | | | | | | 34.85 |
| Vagina..... | | 1.05 | | | | | | | | | | 1.14 |

carcinoma of other organs is shown in the table compiled by von Berencsy and von Wolff:²

It will be seen from an examination of this table that carcinoma of the gall-bladder has a very marked tendency to occur more often in women than in men and that it constitutes in most of the statistics between 8 and 10 per cent. of all carcinomas in women. It would seem fair, therefore, to conclude from the various statistics which have been already presented that carcinoma

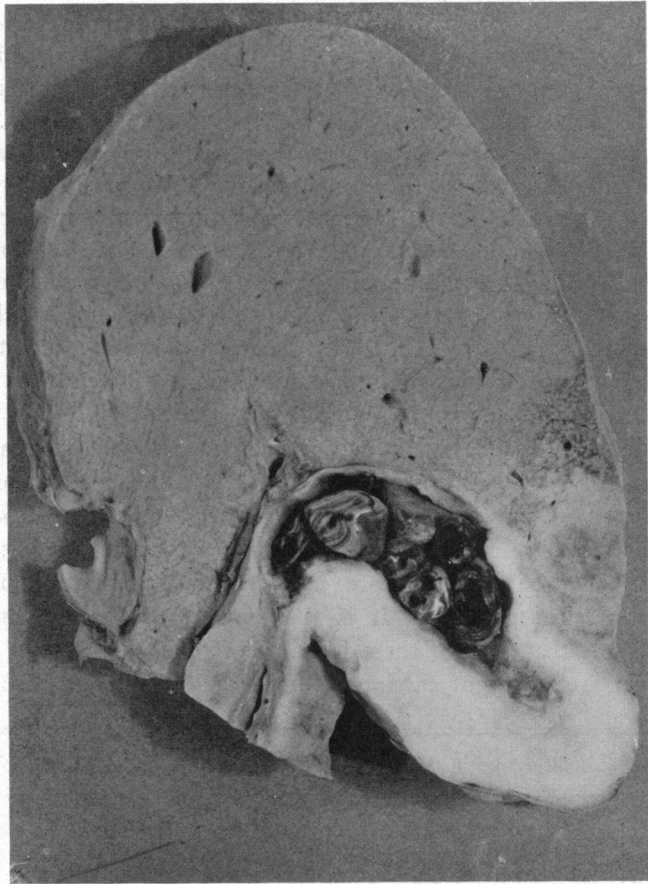


FIG. 1.—A typical example of carcinoma of the gall-bladder associated with calculi.

of the gall-bladder is a comparatively frequent disease and because of that reason deserves our attention.

In this country, also, the frequency of carcinoma of the gall-bladder seems to be about as great as in the table given above. The mortality statistics³ of the Bureau of the Census for 1926 state that in the registration area of continental United States there were, in 1925, 9,558 deaths from cancer of the liver and gall-bladder. In 1926, there were 9,635 deaths. It is true, of course, that all of these deaths were not due to primary carcinoma

PREVENTION OF GALL-BLADDER CARCINOMA

of the gall-bladder, but since other carcinomas which cause metastases to the liver are listed separately under the œsophagus, stomach, intestine and rectum, the presumption is strong that most of these cases listed as carcinoma of the liver and gall-bladder were either primary carcinomas of the gall-bladder or primary carcinomas of the liver. The latter tumor is known to be rare. It would seem fair, therefore, to conclude that the majority of cases listed as carcinoma of the liver and gall-bladder were primary carcinomas of the gall-bladder. Primary carcinoma of the other portions of the bile tract is known to be rare as compared with carcinoma of the gall-bladder. During the same two years, the total deaths from cancer of all kinds were as follows: in 1925, 95,504 deaths, and, in 1926, 99,833 deaths. This would indicate that carcinoma of the gall-bladder constitutes roughly between 8 and 10 per cent. of all carcinomas and that its incidence for the general population is about 9 per 100,000. This is a very considerable number of deaths from this cause. As listed in the mortality statistics, deaths from cancer of the gall-bladder are about three times as frequent as from that of the lip, about one and one-half times as frequent as all cancers of the lip and buccal cavity, about twice as frequent as cancer of the rectum, of about the same frequency as cancer of the breast, about two-thirds as frequent as cancer of the female genital organs, and a little less than one-half as frequent as carcinoma of the stomach. It should not necessarily be inferred from these figures, however, that the occurrence of carcinoma of the gall-bladder in comparison with other organs is actually so high as it would seem to be, because nowadays many people with cancer of the other parts of the body mentioned are cured by surgical and other methods and, therefore, many cases of those cancers would not appear in the mortality statistics. The figures which are given merely show the deaths from the various types of cancer.

Concerning methods of prevention, the most outstanding fact is that carcinoma of the gall-bladder, in the great majority of cases, is associated with gall-stones. The frequency of the relationship between carcinoma of the gall-bladder and gall-stones is so great that various statistical studies have shown that in from 69 (Musser⁴) to 100 per cent. (Janowski⁵) of cases of carcinoma of the gall-bladder, biliary calculi are present. Lentze,⁶ who has recently studied the statistical incidence of gall-stones in cases of carcinoma of the gall-bladder from an extensive review of the literature, considers that cholelithiasis is practically always the primary condition. In this opinion he is not alone. Almost all of those who have studied this question believe that the evidence is overwhelming that when calculi are present they have preceded the development of the carcinoma. They should, therefore, be considered as being a definitely precancerous lesion. It seems unnecessary to present here in a detailed manner all the evidence in favor of this view. It is, perhaps, sufficient to call attention to a few facts. The opinion which has been expressed by some writers that the calculi are the result of the carcinoma seems to be supported by no evidence. For example, Siegert⁷ showed that, although calculi were present in ninety-four cases of a total of

ninety-nine primary carcinomas of the gall-bladder which he collected, they were present in only two of thirteen cases of metastatic involvement of the gall-bladder. Rolleston and McNee⁸ collected twenty-five other cases of metastatic involvement of the gall-bladder and found calculi present in only one. Therefore, in the total of thirty-eight cases of metastatic carcinoma of the gall-bladder, gall-stones were present in only three cases, an incidence of 8 per cent., which is well within the normal limits of incidence of gall-stones. What would seem to be conclusive evidence of the importance of the factor of cholelithiasis in the production of carcinoma of the gall-bladder seems to have been supplied by the experiments of Leitch,⁹ of the London Cancer Hospital Research Institute, who found that when he introduced human gall-stones and even ordinary pebbles into the gall-bladders of guinea-pigs there resulted a remarkable change in the epithelium of many of the cases, which he considered to be entirely characteristic of carcinoma. Although metastases of distant organs did not occur, nevertheless, there was marked invasive growth of the carcinoma into the liver, the omentum and even into the chest wall. The illustrations accompanying Leitch's article are very convincing. It would seem, therefore, that there can be no reasonable doubt that the presence of calculi in the gall-bladder predisposes the individual to a carcinoma of that organ. This would seem to be particularly the case if the patient is a woman beyond the age of forty. It is unnecessary in this article to discuss how the gall-stones may operate to produce the carcinoma.

Another important consideration is the question: In what proportion of cases of cholelithiasis does carcinoma of the gall-bladder occur? The various statistics which have been published on this point vary greatly. Lentze⁶ found, in a collective study, that in 557 cases of cholelithiasis in women over thirty-nine years of age, there was an associated cancer of the gall-bladder in 5.1 per cent. Rolleston* states that 4.5 per cent. of all cases of cholelithiasis are accompanied by carcinoma of the gall-bladder. Moynihan* gives 5 per cent., Riedel* 7 to 8 per cent., Mayo-Robson* 10 per cent., Schröder 14 per cent. In our own cases at the Barnes Hospital 8.5 per cent. of all cases of stones in the gall-bladder have been associated with carcinoma of that organ. According to Leitch, the lowest incidence reported is that of Candler, who found in post-mortem statistics from an insane asylum an incidence of only two cases of carcinoma in 315 cases of calculi. The highest incidence, according to Leitch, is that reported by Slade, who found 30 per cent. It is, of course, probable that the incidence reported by surgeons, and coming from the general hospitals, is somewhat higher than that of the general population, because practically all of the cases of carcinoma of the gall-bladder sooner or later reach the hospitals, but many of the cases of ordinary cholelithiasis without carcinoma do not. It would seem reasonable to conclude, however, that at least 4 or 5 per cent. of women in the cancer age, who have gall-stones, will develop carcinoma of the gall-bladder and

* Quoted from Leitch.

PREVENTION OF GALL-BLADDER CARCINOMA

perhaps further study will show that the incidence may actually be much higher.

If we accept the idea that gall-stones represent a definite precancerous lesion of the gall-bladder, the most obvious consideration in the prevention of this condition is the question of the possibility of diagnosing biliary calculi. The improvement in diagnosis of lesions of the biliary tract, which has been made possible by cholecystography, now enables us to diagnose biliary calculi with practically 100 per cent. of accuracy. It is true that the stones themselves cannot always be visualized, but in our experience at the Barnes Hospital every case of biliary calculi, without exception, which has come to operation, has revealed itself on cholecystographic examination, either by actual visualization of the calculi or by the demonstration of an unquestionably pathological gall-bladder. It would seem, therefore, that no particular difficulty should be encountered in the recognition of this very definite precancerous lesion.

A most important consideration is, of course, the question as to whether or not we should advise the operative removal of a calculous gall-bladder, or at least of its contained stones, from the point of view of cancer prevention entirely apart from the other more usual operative indications. This question naturally involves the consideration of the risk of cancer on the one hand as compared with the risk of operation on the other. The operative mortality in uncomplicated cases of cholelithiasis before there has been much damage to the liver, to the heart, to the kidneys, *etc.*, should not be more than 1 per cent. This is, approximately, one-fourth or one-fifth of the danger of death from carcinoma. At the hands of experienced surgeons, the operative mortality, even including all of the bad risks which present themselves as examples of long-neglected biliary-tract disease with many incurable complications, is still about only 3 per cent. or less. Our own mortality at the Barnes Hospital during the last three years has been 1.5 per cent. This series has included patients of all ages and with practically all of the known complications of biliary-tract disease. Deaths from all causes which have occurred in the hospital have been included in the operative mortality. It is significant, however, that most of the deaths have been due to incurable complications of neglected disease of the biliary tract. Younger patients, in better physical condition and with fewer complications, would almost certainly present a much lower operative mortality. From the standpoint of cancer prevention, it would seem to be our duty to inform patients with gall-stones that, in general, they have a greater chance of dying from carcinoma of the gall-bladder than they would have by a properly performed operation. This phase of the question is in addition to any other features of the case which should be regarded as ordinary indications for operation. The danger of cancer is especially great in women past forty, and this danger is probably increased if they come from cancer families with an inherited predisposition to its development.

SUMMARY

Since gall-stones seem to have an etiological relationship to the development of carcinoma of the gall-bladder in nearly all cases, the occurrence of most if not all cases of carcinoma of the gall-bladder could be prevented by cholecystectomy in cases which present evidence of gall-stones, regardless of the presence of those symptoms which would ordinarily compel a patient to have an operation. The diagnosis of gall-stones is now easily and accurately made by cholecystography. In uncomplicated cases of gall-stones there is less risk of death from the operation of cholecystectomy than from the development of a carcinoma of the gall-bladder, particularly if the patient is a woman of middle age. Contrary to the general opinion carcinoma of the gall-bladder is not a rare disease, but a very common one. It constitutes approximately 8 or 10 per cent. of all carcinomas.

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