GUEST EDITORIAL

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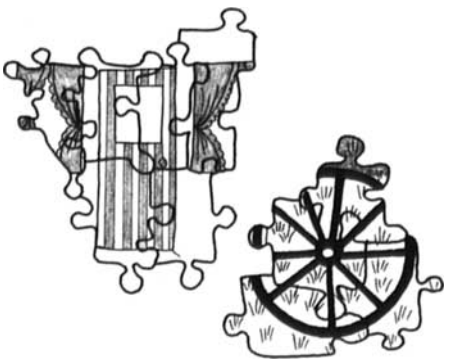
Large-Bowel Cancer: An Epidemiologic Jigsaw Puzzle

THE MANY FRAGMENTS of available knowledge regarding cancer of the large bowel lie scattered like pieces of a giant jigsaw puzzle awaiting assembly. If they could be correctly pieced together, the pattern emerging might well provide clues to the causation of this increasingly common tumor and lead to preventive measures that would save many lives and untold suffering. Epidemiologic evidence strongly suggests that bowel cancer—the second commonest cause of cancer death in the Western world after lung cancer—is very much dependent on man-made environmental factors and therefore is potentially largely preventable.

Faced with such a problem, we must relate the fragments of available evidence to one another and postulate some hypothesis for the cause of these tumors. New facts as they come to light can then be related to this hypothesis which may thereby be disproved, modified, or substantiated. Such an approach is similar to the attempted assembly of the jumbled pieces of a jigsaw puzzle. Initially, as many puzzle pieces as possible are fitted together (text-fig. 1), which corresponds to the assembly of known facts; with this as a base, imagination is now needed to formulate a hypothesis as to what the completed picture might be. The fragment of the picture so far available suggests that the whole may include a stagecoach (text-fig. 2). Some new evidence, again represented by a jigsaw fragment, may be inconsistent with the hypothesis provisionally formulated, the piece not fitting into the imagined picture (text-fig. 2). All too often the sponsor retains his particularly treasured hypothesis by sweeping the inappropriate information under the carpet, rather than respecting the evidence and, as must be done, substituting a new hypothesis both faithful to the facts already assembled and accommodating the new evidence. Thus the wheel is seen as possibly belonging to a penny-farthing bicycle and the door and windows as part of a cottage (text-fig. 3). The new piece has now found its place in the projected whole.



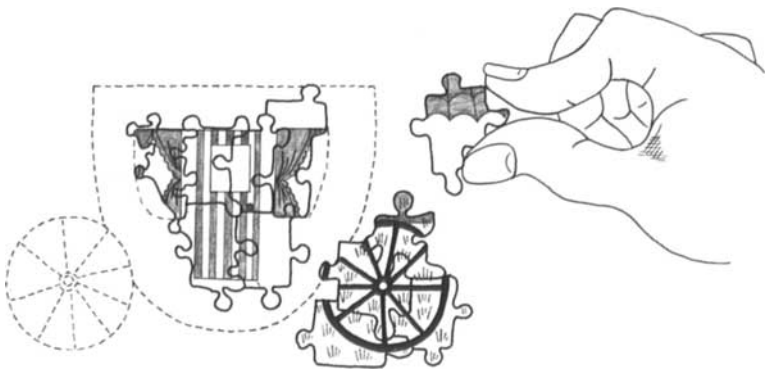
TEXT-FIGURE 1.—Available facts marshaled as pieces of a jigsaw puzzle assembled as far as possible.

Just such a change of interpretation of facts became necessary in the light of new evidence during my investigation into the disease which, by the generosity of former colleagues, is now known as Burkitt's lymphoma. The earlier and admittedly attractive hypothesis which visualized a vectored virus as the agent responsible for the cancer had to be abandoned in the face of evidence inconsistent with such a picture. This was replaced by an alternative concept which incriminated malaria as a cofactor, a change corresponding to replacement of the imagined carriage by the cottage and bicycle in the jigsaw puzzle. If further facts, the jigsaw pieces, continue to fit into place, the hypothesis will become a theory and the theory a fact (text-fig. 4).

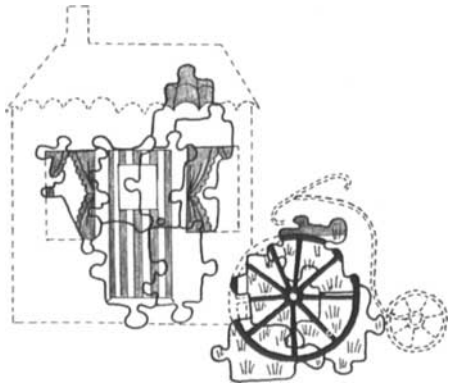
THE PUZZLE PIECES

For large-bowel cancer, the box of puzzle pieces contains to date the following facts, but there are

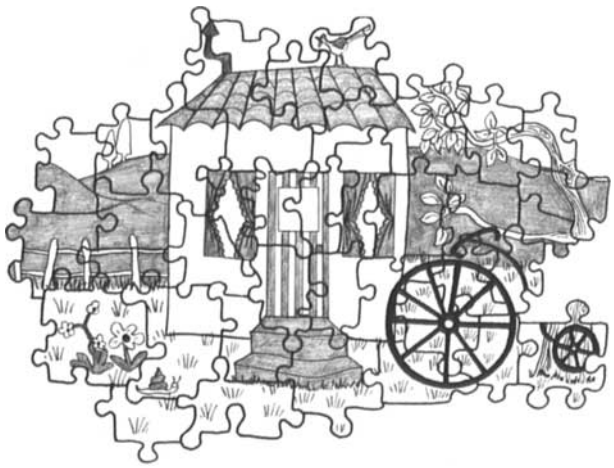
Editor's note: Periodically the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the causes or cure of cancer.



TEXT-FIGURE 2.—Construction of a hypothesis. A jigsaw puzzle fragment, or newly discovered fact, fails to fit.



TEXT-FIGURE 3.—Erection of a new hypothesis that accommodates the new fact.



TEXT-FIGURE 4.—Completing the puzzle or converting hypothesis into fact.

doubtless many other pieces as yet undiscovered. If these available pieces could be meaningfully assembled, a hypothesis could be formulated that should make it easier to search for the still missing fragments.

1) There is a close epidemiologic association between cancer of the colon and of the rectum. Both tumors have their maximum and their minimum incidence in the same populations. Variations in incidence of cancer of the colon and rectum (combined) among communities in different parts of the world are nearly four times greater than the variations in the proportion at which either site is affected relative to the other (*1*). This suggests some environmental factor(s) common to tumors in both sites, with modifying factors accounting for changes in relative proportions in different areas.

2) Cancer and adenomatous polyps are closely associated *a*) in their geographic distribution (*2*); *b*) in their anatomic distribution (*3*); *c*) in individual patients (*4*); *d*) in age distribution of the patients (*3*); and *e*) in their experimental induction (*5*). These observations suggest some causative factor common to both the benign and the malignant lesions.

3) Although the mucosal area in the small bowel is over 100 times greater than that of the large bowel, epithelial tumors are much more than 100 times commoner in the large bowel; thus, relative to surface area, the large-bowel mucosa is more than 10,000 times more liable to develop cancer, and probably in Western countries over 100,000 times more liable to grow adenomatous polyps, than is that of the small intestine. This may be partly explained by a greater susceptibility of the large-bowel mucosa to noxious elements in the fecal stream, but it suggests that the carcinogenic agent is either formed or activated in the large bowel rather than ingested in an active form in the food.

4) Anatomically, most of both the benign and the malignant tumors occur in the areas of the bowel where the feces tend to stagnate, at the beginning of the ascending colon and in the distal colon and rectum. This suggests a relationship between tumor induction and prolonged contact between the feces and the bowel mucosa.

5) The prevalence of tumors of the large bowel is closely associated with economic development (*2*) and with urban as contrasted with rural life (*6*). This suggests that both Western and, in particular, urban influences increase the carcinogenic factor that presumably resides in the feces.

6) The prevalence increases on migration from a less-westernized to a more-westernized country (*7*). This emphasizes the environmental dependence which is probably diet related.

7) Some 40 or more years ago the prevalence in U.S. Negroes was significantly less than that in U.S.

Caucasians (*8*), a discrepancy which has since disappeared. This suggests that changes in habits of Negroes over the past 40 years have increased the potentially carcinogenic factor in their feces more than have any changes in the customs of Caucasians over the same period.

8) The mucosa of the large bowel is more likely to be the site of multiple tumors than is any other body structure except the skin. In Caucasians, all of the skin surface excessively exposed to sunlight is liable to cancerous change and tumors are consequently multiple. The tendency to multiplicity of bowel tumors is consistent with a hypothesis of exposure of the whole mucosa to potentially carcinogenic stimuli.

9) Carcinogens that induce tumors in normal rats fail to do so when the rats are maintained in a sterile environment (*9*). This indicates that bacteria play a vital role in the carcinogenesis.

10) The feces from populations with a high risk of bowel cancer contain more anaerobes, particularly of the bacteroides group, than do the feces from people of low-risk areas. The bacteroides are active in degrading the bile acid cholate to deoxycholate (*10*, *11*). This further suggests that fecal bacteria play an important role in human bowel cancer and that the bacterial degradation of the bile acid cholate to potentially carcinogenic deoxycholate may be particularly significant. It is not yet certain whether deoxycholate is carcinogenic or whether it merely acts as an index of bacterial activity producing other potentially carcinogenic agents.

11) The addition to diet of fiber in the form of bran inhibits the bacterial degradation of cholate (*12*). This would indicate that the removal of cereal fiber from diet enhances bacterial degradation of cholate and therefore possibly also of other fecal constituents.

12) It has been suggested that fat alters fecal bacteria (*13*). It is known that changes in dietary fiber do this, as does intestinal obstruction.

13) Large-bowel cancer is largely a disease of later life, with an age distribution among patients similar to that of diverticular disease and hiatus hernia. This is consistent with a hypothesis that these diseases result from low-intensity or oft-repeated stimuli over a long period.

14) A number of diseases are more or less closely associated epidemiologically with large-bowel tumors, both in geographic distribution and in chronologic time of emergence as clinical problems. These include diverticular disease of the colon, cholesterol gallstones, ischemic heart disease, and hiatus hernia. Appendicitis is related, in that its prevalence has risen significantly in all communities examined several decades before any significant rise in the prevalence of the other diseases listed above (*14–17*). A good correlation has been shown between the incidence of colon cancer and of ischemic heart disease in different countries (*18*). These observations suggest that some common factor(s) has a causative function in each of these diseases.

15) Populations with relatively short intestinal transit times and with large soft stools containing low concentrations of degraded bile acids have a low prevalence of large-bowel tumors and their associated diseases. One apparent exception with regard to transit times has been reported from Hawaii, but neither the weight nor consistency of the stools was recorded (*19*). On the other hand, communities with prolonged transit times, small firm stools, and high fecal concentrations of degraded bile acids have a higher prevalence of large-bowel tumors and their associated diseases. This suggests that the factor partly responsible for these diseases acts by influencing the behavior of the gastrointestinal tract, slowing the fecal stream, producing small firm stools, and increasing bile acid degradation.

16) Intestinal transit times and stool weights and consistency are directly related to the fiber content of the diet (*20*).

17) Vegetarians in North America tend to have a lower risk of developing bowel cancer or ischemic heart disease than do nonvegetarians (*21*). This would be consistent with a causative function of meat or fat or a protective role of plant foods.

FORMULATING A HYPOTHESIS OR ASSEMBLING THE JIGSAW PUZZLE

The evidence outlined above would appear to suggest that large-bowel tumors are related to some factors characteristic of modern Western society, which slow down intestinal transit times, produce small firm stools, and alter the fecal bacterial flora. The role of these factors in the diseases associated with bowel cancer must also be postulated.

One such factor could be the lower consumption of dietary fiber, due mainly to the greater refining of flour and sugar, and also to the reduced intake of potatoes and legumes. The fiber in fruits and green vegetables is less effective, since it is more diluted and large quantities of those foods are apparently necessary if they are to compensate for these changes.

Not only are fiber-depleted diets known to slow intestinal transit times and reduce stool weights, but also they have a profound effect on cholesterol and bile acid metabolism; this has been postulated to be important in the pathogenesis of both cholesterol gallstones (*22*) and ischemic heart disease (*23*).

Whether or not changes in bacterial flora derive from changes in dietary fat or dietary fiber, the retarded bowel function associated with fiber-depleted diets provides additional time for *a*) bacterial proliferation and *b*) degradation by bacteria of bile acids.

Moreover, since addition of fiber appears to suppress bacterial degradation of bile acids (*24*), its removal must be assumed to accelerate the process.

Thus formation of more potential carcinogens may be expected with low-fiber diets, and any carcinogens so formed will be held for a prolonged time against the bowel mucosa, concentrated in a small fecal mass.

It is known that the pattern of fecal bacteria is related both to diet and to prevalence of bowel cancer.

It is known that certain anaerobes more prevalent in stools of Western populations can convert bile acids into deoxycholate and lithocholate, and glucuronide conjugates into cuprastanol and cuprastanone.

It is also known that the bacterial degradation of cholate to deoxycholate is suppressed by the addition of cereal fiber to the diet and is therefore presumably enhanced by the removal of such fiber.

It is known that fiber-depleted diets prolong intestinal transit times and consequently provide more time for bacterial activity and for the action on the bowel mucosa of any carcinogens present in the feces. It is also known that such diets concentrate fecal constituents, including any potential carcinogens, and thus presumably enhance their action.

It is not known that changes in diet alter the fecal bacteria, and there is some uncertainty as to what dietary components influence bile secretion.

The association between bowel tumors and diverticular disease could be accounted for by the fact that the fecal stasis associated with low-fiber diets results in raised intraluminal pressures that force the mucosa out between the muscle bundles in the bowel wall (*25*, *26*). The association with hiatus hernia is consistent with the only hypothesis of causation fitting the epidemiologic evidence; i.e., straining at constipated stoools may be the fundamental cause of oft-repeated intra-abdominal pressure forcing the stomach upward through the esophageal hiatus (*16*).

The consumption of fat or other postulated agents such as beef could, with fiber depletion, be cofactors, but these fail to account for the associations between large-bowel cancer and some other characteristically Western diseases.

PRACTICAL CONSIDERATIONS

The restoration of dietary fiber in the form of whole-meal bread (5 oz contains 2 g) and the addition of cereal fiber in the form of bran (2 dessertspoonsful = 2 g) quickly revolutionize bowel habits. Apart from some increase in flatus in the initial stages, ill effects are nil. There is much—we do not yet know how much—to be gained by this change, and nothing to be lost, so the betting odds are good: "Heads I win and tails I don't lose."

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