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Synchronous and metachronous carcinoma of the colon and rectum

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Sir Hugh spent much of his retirement at Hannington near Basingstoke, and took great pleasure in contributing to the work of our hospital. When he died, one of the great dynasties of British colorectal surgery passed into history, for he and his father, J P Lockhart-Mummery, must certainly be on the short-list for the most distinguished father and son team of the twentieth century. His father had views on multiple malignancies of the large bowel which aroused Sir Hugh's curiosity and which led to his asking me to gather together, with the help and guidance of Dick Bussey, the St Mark's Hospital data on all those patients who had developed more than one colorectal carcinoma.

Lockhart-Mummery, senior, published what was probably the first surgical account of family adenomatosis in 1925 *(1)* and concluded his paper with the following summary:

1 Adenomatosis of the large bowel is a condition which tends to develop in succeeding generations of the same family.
2 Individuals with multiple adenomata of the large bowel almost invariably develop cancer in one or more of the adenomata after a few years.
3 The members of families with a hereditary tendency to multiple adenomata tend to die of cancer of the large bowel, and at an early age.

Fourteen years later he amplified this account in a paper published with Cuthbert Dukes in the *Lancet (2)*. This second paper included reports of five patients treated by total excision of the colon, four of whom were apparently cured.

Turning to multiple primaries without adenomatosis, it is interesting to note that 'JP' thought, as did most others in the first half of the century, that the presence of one bowel cancer had an inhibitory effect upon the development of another. It later became clear that the incidence of multicentre colorectal primaries is higher than would be expected by chance *(3,4)*. Wide variations in the incidence are quoted in the literature, from 1.8% to 9.8% of cases *(5,6)*. At the Mayo Clinic, Moertel *et al. (7,8)* reported the incidence of multicentric large bowel cancers to be 4.3% compared with an incidence of 5.1% for multiple primary cancer at all sites.

Sir Hugh and I reviewed the records of St Mark's Hospital for synchronous cancer of the bowel and for metachronous cancer of the bowel *(9,10)*. Our figures have since been updated *(11)*, but I hope you will forgive me for quoting our original figures on this occasion. Of 4884 survivors from operations for cancers of the large bowel (apart from those associated with major polyposis or colitis), 83 of the operations (1.6%) were for second, ie metachronous growths. A synchronous growth was found at or within 1 month of operation in 157 patients (3%), nearly double the incidence of metachronous cancers in the same series. However, the true incidence is probably greater, since 18 of those classified as metachronous were present at the time of the original operation. They were really 'missed synchronous' growths.

The true incidence of synchronous cancer, therefore, was about 3.5% (which accords with many other published series) and this is almost exactly the same figure as the cumulative long-term risk in our series of developing metachronous cancer. Thus, when we diagnose colonic or rectal cancer, there is a 3.5% risk that a second cancer is present at the same time; and if we cure the patient, there is a further 3.5% risk that another cancer will develop over the years.

Triple carcinoma was observed in less than 0.25% of the operations at St Mark's Hospital. The Mayo Clinic series had a slightly higher incidence of third tumours in that 11% of those patients having surgery for metachronous tumours subsequently required operation for a third cancer *(12)*.

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Only the second of Billroth's postulates *(13)* is necessary for stating that two primary tumours coexist in the bowel (ie that they can be clearly identified both macroscopically and microscopically as arising in different locations). Histologically, most large bowel tumours have many similarities, although variations in the degree of differentiation are common within and between tumours. Similarly, metastases from one lesion are unlikely to be recognisably different from those of another. Distinguishing a second primary growth from local recurrence of a previously excised cancer is not usually difficult. The second primary arises on the mucosal surface of the bowel and invades outwards, ie it has a characteristic appearance both macroscopically and microscopically. Conversely, even a small suture-line recurrence usually appears to arise outside the bowel and only secondarily invades towards the lumen.

Timing, site and stage

In the St Mark's series, the average interval between the first and second operation was just over 11 years. In the Mayo Clinic series, 50% of the patients had their second operation within 5.5 years of the first *(1,2)*. The low incidence in the first 5 years probably reflects the selection of patients with a 'clean colon' by the first operation and by the exclusion of the 'missed synchronous' cancers. The subsequent rise in the incidence may simply be the result of increasing age of the survivors.

The site of the second cancer in the St Mark's series showed approximately the same pattern of distribution as did single cancers. However, in the Mayo Clinic series, the proportion of carcinomas in the right colon rose from 21% for first cancers to 48% for second lesions.

Bussey *et al. (14)* reported that the histopathological grade of the first growth in the St Mark's metachronous cancer series tended to be unusually favourable. This is probably because there are more long-term survivors from less malignant and less advanced growths, but does not necessarily imply an intrinsic tendency for multiple growths to be more benign. However, there is a suggestion that second growths appear somewhat more favourable in stage than would be expected in 'first-time' cancers and perhaps this was the trend which 'JP' had observed. The higher proportion of stage A tumours probably reflects the value of careful follow-up in detecting such lesions, for second tumours discovered presymptomatically were found to be more favourable than those with symptoms.

Association with benign disease

The association between benign adenoma and bowel cancer is well documented and adenomatous polyps increase the risk of developing cancer by five times *(15)*. In the St Mark's series, two-thirds of all multiple cancers showed evidence of associated benign lesions at a time which largely antedated the use of the colonoscope. We found that more than one-half had adenomas and about one-tenth had villous lesions. This incidence is three times that found in resection specimens for single cancers, and more than ten times that in the population as a whole. In approximately one-quarter of these, the malignancy was actually identified as arising within a pre-existing benign tumour.

The Mayo Clinic series shows a similar trend, but a lower figure (40%) for associated benign lesions *(12)*. Futhermore, if adenomas are identified on an operation specimen in association with a cancer, Bussey *et al. (14)* showed that the risk of developing a subsequent cancer was doubled. All this evidence linked colorectal multiple malignancy with benign tumours of the large bowel epithelium, and reinforced the observation of Morson *(16)* that the adenoma–cancer sequence is important in the genesis of large bowel malignancy.

Management of multiple tumours

The management of polyps is by endoscopic excision and that of cancer is by excision of the relevant segment of bowel with its mesentery. The extent of the operation when two cancers have been discovered will be a matter for individual choice. St Mark's surgeons had elected to use a conservative approach, each growth being resected in a radical fashion but normal colon being retained where possible. Thus, right hemicolectomy and an anterior resection might be combined in a single patient.

More extensive colonic resections have many advocates in the United States. The cumulative risk that survivors will develop a metachronous growth rises from about 3.5% after resection of a single cancer to more than 8% after removal of two growths. However, the time interval is around 13 years, and there is a strong argument for conservative surgery backed by careful follow-up. The increased morbidity (and perhaps mortality) of total colectomy must be weighed against the risk of developing a subsequent cancer which will have a very good chance of cure provided it is detected early. The ready availability of colonoscopy makes this view more rather than less valid for the 1990s. The reverse argument was propounded by Wangensteen as long ago as 1943 *(17)*, and recently reiterated by Fagler and Weiner in 1980 *(18)*. The extirpative approach finds wide acceptance by surgeons in the United States. They point to the ever-rising incidence of multiple lesions if they are searched for by colonoscopy, a preoperative investigation which they now regard as mandatory. They would not hesitate to perform subtotal colectomy in every case of multiple malignancy, and some imply that we should be moving towards subtotal colectomy for every colorectal cancer.

Few British surgeons accept these arguments for the long-term morbidity of ileo-anal anastomosis is unacceptably high. Although ileal pouch operations to reduce stool frequency are now well established on both sides of the Atlantic, they are formidable surgical undertakings and their widespread introduction outside centres of special interest would undoubtedly lead to

fatalities. Furthermore, the stool frequency is an unacceptably high price to pay for the avoidance of stringent follow-up.

Sir Hugh remained conservative; each cancer should be managed as if it were a single lesion, and multiplicity constituted an indication for rigorous follow-up.

Follow-up and metachronous cancer

Detection of metachronous cancer is probably the most valuable aspect of a follow-up clinic and the colonoscope has revolutionised the routine examination. First-class double contrast radiology can produce comparable pick-up rates for the larger lesions but the tiny adenoma is easily missed. Furthermore, the colonoscope is able to deal with the lesions as they are found and the examination is considerably facilitated by the absence of the sigmoid loop after left-sided excision.

Sir Hugh considered that colonoscopy probably does not need to be more frequent than once in 2 to 3 years as Morson showed that the polyp–cancer sequence is usually spread over many years *(19)*. A good view of the whole colonic mucosa can lead to the assumption that the patient is 'safe' for a considerable time, but a really good view is essential.

Prognosis after treatment

For synchronous cancers, the operability rate of 82% for radical resections was higher than the corresponding St Mark's figure of 68% over the same period for single rectal cancers. The corrected 5-year survival rate for radical resection was 66%. Thus, one can say that four of five patients were operable, and that two out of three of these were cured of both growths by the operation. These figures are certainly no worse than those in most comparable series of single cancers, and even suggest that a patient with two colorectal cancers fares slightly better than a patient with only one—perhaps 'JP' was right?

Examination of the 5-year survivals by stage, demonstrates the expected distribution of cures. Patients with two Dukes' B or two Dukes' C growths do not show the adverse effect that might be expected if the malignant potential of the two were to summate, ie if one B tumour had, say, a 50% chance of killing the patient then two Bs might be expected to give 75% risk. In the event, it is not so, but still 50%. This observation has aroused little interest, but it seemed to Sir Hugh to demand some biological or immunological explanation. Similar favourable information about the excised second tumours was obtained from the histopathological data in the St Mark's metachronous group, and the nine cases of triple synchronous carcinoma in this series showed the same favourable trend. Four of the eight survivors lived for more than 10 years, and the average survival time for all resections, including one classified as palliative, was 7 years and 8 months; this is almost exactly the average for single cancers.

Perhaps these strangely favourable trends indicate some important message. Sir Hugh, or Lyn as he was more affectionately known, contemplated the problem with pleasure as being (one of his favourite phrases) of 'baffling simplicity'.

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