RECTAL CANCER AND PRESERVATION OF FUNCTION*

BY

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No single standard operation is suitable for all cases of rectal or recto-sigmoid cancer, for the operation should be planned to suit the rectum rather than the rectum cut to suit the plan. The ideal is the efficient removal of the growth with preservation of normal defaecation. A permanent colostomy is not too high a price to pay for the efficient removal of a rectal cancer provided it is essential; it is a heavy burden if it is not. Clinical surgery suggests, and pathology supports the view, that in a number of these cases the internal sphincter, that mechanism of continent defaecation, is needlessly sacrificed through devotion to a stereotyped operation. At the same time it is salutary to remember that some surgeons have in the past abandoned anastomotic operations through the fear and the experience that such methods sometimes lead to an inefficient extirpation of the growth.

History

An operation to excise a rectal growth and preserve a functioning anus is no novelty; it is probable that it was a more fashionable ambition for the surgeon in the past century than it is now. Even a brief study of the literature on this subject makes it apparent that it would now be almost impossible to devise a truly original operation of this type, save perhaps in its minor details. The ingenuity of many surgeons has explored every conceivable route. Extensive reviews of the literature have been made by Bacon (1945), d'Allaines (1946), and many others. It will suffice here to mention some of the methods which seem to have influenced the present trend of surgical opinion.

It was not until the latter part of the last century that excision of the rectum became common. Though not the first, one of the more interesting of the early attempts to perform a resection-anastomosis on a rectal growth is that described by Maunsell in 1892. The rectum was mobilized through the abdomen and was then prolapsed through a dilated anal orifice to an assistant working in the perineum, who divided the outer layer of the prolapse, pulled down the growth, and performed a resection-anastomosis. Maunsell's immediate post-operative treatment consisted in making his patients drink large quantities of hot water, for he had found that he "had more success with hot water than with any other remedy." However unusual the post-operative treatment of half a century ago may seem to-day, the steps which Maunsell described have been the basis for many subsequent methods. Rayner (1935) quotes Sebrecht as utilizing the abdominal mobilization followed by the dissection upwards of the rectal mucosa from the mucocutaneous junction and the suture of the sigmoid to the anal canal. In 1908 Miles introduced the abdomino-perineal operation, and this discouraged attempts to restore anal function, at least in this country. In 1932 Babcock described the operation of procto-sigmoidectomy without preliminary colostomy, the salient features being the abdominal mobilization, excision of the lymphatic field at a high level, the perineal approach from within the external sphincter, and the removal of the internal sphincter, the sigmoid being brought out as a terminal colostomy through

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the anus. Devine (1937) advocated a preliminary transverse colostomy followed by resection and anastomosis on a clean and empty bowel. Dixon (1944) and Wangenstein (1945) have adopted a purely abdominal approach in suitable cases. Lockhart Mummery (1908), Pannett (1935), and others have described combinations of the abdominal and perineal approach, and Lloyd-Davies (1939) has described a "pull-through" method with drainage of the presacral space through the anastomotic line.

It will be apparent from even this superficial survey that the surgeon who essays resection and anastomosis for a rectal growth has a wide choice of operation. Fortunately it is no shame to follow another's path: to be original it is necessary only to think for oneself and not necessarily unlike everyone else. He who constantly performs the same operation sometimes acquires not only dexterity in his particular method but a reluctance to attempt another. Certain aspects of this type of operation require special consideration; from these we must draw our personal conclusions.

The Sphincter Mechanism

Milligan and Morgan (1934) have made a careful study of the internal and external sphincters, and it is generally accepted that perfect continence requires an intact ano-rectal ring—that condensation of the circular muscle fibres of the rectum in association with the pubo-rectalis fibres of the levator ani muscle. It is true that Bacon and Babcock rely on the external sphincter for control after procto-sigmoidectomy, sutured round the sigmoid colon two to four weeks after resection. They state that 80% of their patients may be classified as continent, though 40% wear a protective perineal pad. While there can be no doubt that a varying degree of control may be obtained from the external sphincter even after it has been divided and repaired, certain continence requires an intact ano-rectal ring and, since the sense of perception is important, an intact lining to the anal canal. A good abdominal colostomy is probably better than an incontinent or untrustworthy anus.

Essential Pathological Requirements

We owe to Miles the first sound description of the pathology of rectal cancer and its implications on its surgical removal. He stressed the lymphatic spread upwards in association with the superior haemorrhoidal artery, laterally with the middle haemorrhoidal vessels, and downwards with the inferior haemorrhoidal vessels. Subsequent pathological studies, while bearing out the importance of the upward spread, have shown that Miles laid undue stress on the frequency of lateral and downward lymphatic spread. The work of Gabriel, Dukes, and Bussey (1935), Gilchrist and David (1938), and Collier, Kay, and McIntyre (1940) has shown that the main lymphatic spread of rectal cancer is in an upward direction, lateral and downward spread taking place only when the lymphatic system above is blocked by growth. Few lymphatic glands over 1 in. (2.5 cm.) below a rectal growth are likely to contain metastases, still less those 2 in. (5 cm.) below, and it would seem to be a reasonable conjecture that a distance of 2½ to 3 in. (6.25 to 7.5 cm.) below a growth is outside its lymphatic spread except in advanced cases. Here the involvement of the glands above the growth is likely to be such that complete removal of infected glands is impossible and any retrograde spread will be of secondary importance.

Dukes (1944) has demonstrated that 17% of rectal growths excised show involvement of the adjacent veins, though this does not necessarily denote hepatic metastases. He has also shown that the cancer cells may grow down the lumen of a vein in a retrograde manner, appearing sometimes as

a nodule of carcinoma in the mucosa below a growth. While this retrograde venous spread is probably uncommon, and such cases must inevitably have a rather poor prognosis, it is an additional reason for removing a margin of normal bowel below a growth.

There is a further pathological consideration to an operation of anastomosis. It is well known that adenomata are often found in the neighbourhood of a rectal cancer, and two primary growths are not uncommon. Some years ago, when pointing out the advantages of a purely abdominal resection for recto-sigmoid and high rectal growths in infirm patients, I drew attention to the possibility of another growth developing in the rectal stump (Muir, 1939). Gabriel and others have since recorded cases in which a carcinoma developed in this site after an abdominal excision. An abdomino-perineal or other combined operation removes completely the rectum and the greater part of the sigmoid colon, but the surgeon who performs an anastomotic operation must bear in mind the possibility, however small, of another primary growth developing from an adenoma in the rectal stump, or indeed in the remaining portion of the sigmoid colon. It is probable that the majority of patients would prefer to accept this risk rather than a permanent colostomy, but the presence of numerous adenomata below a high rectal growth should be regarded as a contraindication to the retention of any rectal mucosa and therefore to an anastomotic operation. The removal of all rectal mucosa, while it has other disadvantages, is in this respect a point in favour of the Babcock-Bacon operation.

The essential pathological requirements for an anastomotic operation are that the lymphatic drainage system of the rectum must be removed at its highest practical level by ligation of the inferior mesenteric artery either between the sigmoid branches or immediately below the last sigmoid branch; that the division of the bowel must be at least $2\frac{1}{2}$ to 3 in. below the growth; and that the presence of numerous adenomata below the growth contraindicates this type of operation.

There are perhaps two occasional exceptions to these rules: the operable growth with small hepatic metastases, and the small growth in the rectal ampulla which clinically appears to be an "A" case. In both these cases there are strong grounds for trying to preserve a functioning anus even if such methods of resection necessitate a reduction in the margin of normal bowel below the growth.

Frequency of Cases Suitable for Resection-anastomosis

Bacon, analysing the site of the growth in 1,401 cases of rectal, recto-sigmoid, and sigmoid carcinomata, considered that over 80% were suitable for resection with preservation of a functioning anus. It should be remembered when considering these figures that Bacon accepts every growth 3 cm. above the ano-rectal line or 6 cm. above the anal margin as suitable for procto-sigmoidectomy, that the internal sphincter is not preserved in this operation, and that sigmoid growths are included in this series. Such sigmoid growths might well be those requiring ligation of the inferior mesenteric artery for their proper removal, but even if they (315) are excluded, 1,086 cases of rectal and recto-sigmoid cancer remain. Of these, 231 were recto-sigmoid, 148 5 in. (12.5 cm.) and 211 4 in. (10 cm.) from the ano-rectal line. Thus 590, or more than half, might appear suitable, at least in theory, for a method of resection-anastomosis which preserved the internal sphincter.

Clinically, growths just palpable at the tip of the finger or discovered only on sigmoidoscopy are usually suitable. The prolapse of a recto-sigmoid growth may be misleading.

A growth 2 to 3 in. above the cervix or vesicles may appear suitable, but in many cases a final decision can be made only at laparotomy. The rectum is not a straight tube, but undulates from side to side, lying curved in the hollow of the sacrum; a growth easily accessible on rectal examination may lie at the level of the abdominal wall when the rectum has been fully mobilized. In general, apart from being operable, growths suitable for these operations should lie at least 2 to 3 in. (5-7.5 cm.) above the lowest level of peritoneal reflection in the pouch of Douglas, though this peritoneal level is by no means constant in its distance from the ano-rectal ring. Growths of the rectal ampulla are unsuitable for operations of this type.

The Sigmoid Colon

Since it is necessary to ligate the inferior mesenteric artery either above or immediately below the last sigmoid branch, the blood supply to the distal sigmoid may be jeopardized. In one of my cases, intended for an anastomotic operation, ligation obliterated the arterial supply to the greater part of the sigmoid, and it became necessary to perform an abdomino-perineal resection. A good blood supply is essential to that part of the sigmoid which is to be brought down to the rectal stump or anal canal. After ligation some surgeons have advised marking the most distal part of the sigmoid with visible pulsation by means of a silk stitch. Poor vascularity is associated with infection and is far less likely to cause trouble when no actual suturing is used, as in "procto-sigmoidectomy," or when the operation is performed on a clean, empty, and non-functioning bowel.

A long and mobile sigmoid is of great assistance: an unusually short bowel or diverticulitis may render the operation impossible. The length of the sigmoid is of more importance in a "pull-through" method than in a purely abdominal resection and anastomosis, when sufficient bowel can usually be obtained by mobilizing it in the left iliac fossa. A pre-operative estimate of the length and condition of the sigmoid can be obtained by a barium enema.

Preliminary Colostomy

A preliminary transverse colostomy, as advocated by Devine, permits the operation to be performed on a non-functioning and, through the use of lavage and sulphaphthaladine, an almost sterile bowel. A left iliac colostomy "takes in slack" and reduces the mobility of the sigmoid.

A preliminary colostomy is not a routine in all methods. It is unnecessary in the Babcock-Bacon technique, where a terminal colostomy is established through the anus without bowel-suturing. Nor is it used by Wangenstein in his method of abdominal resection and anastomosis, employing deep pelvic clamps. d'Allaines performs colostomy at the time of the resection, on the grounds that a defunctionalized bowel is shorter, shrunken, and more difficult to anastomose.

Necrosis and infection are not only more likely but are also more dangerous when they occur in functional bowel. A preliminary colostomy will require closure, and its use may add three to four weeks to a patient's stay in hospital, but it adds such a degree of safety to these operations that I regard it as essential.

The Route

The necessity for removing the lymphatic field at its highest level makes abdominal mobilization an essential part of the operation. The resection may be carried out from the abdomen alone, thus requiring an anastomosis

between the sigmoid and the rectal stump in the depths of the pelvis, or the abdominal mobilization may be combined with a perineal anastomosis. This may be performed above the levator muscles, aided by their partial division, or outside the anal canal, by prolapsing the rectum, the growth, and the sigmoid through a dilated anus. Finally, as in procto-sigmoidectomy, the sigmoid may be brought out as a terminal colostomy through the anal orifice. My personal choice is for two methods: abdominal resection and anastomosis without clamps, which I believe to be applicable to the majority of suitable cases, and a "pull-through" resection, which, at least in my hands, requires a long sigmoid.

Abdominal Resection and Anastomosis without Clamps.

—The use of clamps deep in the pelvis presents considerable difficulties. I have not had the opportunity of using those devised by Wangenstein for this purpose, but any clamp in this situation takes up valuable room and leaves devitalized tissues. I think it is therefore preferable to dispense with clamps for the purpose of the anastomosis. This operation is suitable for recto-sigmoid growths and many of those in the upper third of the rectum. A preliminary transverse colostomy is performed 14 days before the resection (combined with laparotomy if there is any doubt whether the case is suitable) and the distal bowel cleared by wash-outs and sulphaphthaladine emulsion. The first step in the resection consists in placing the patient in the lithotomy position and carefully swabbing out the rectum. The coccyx is removed and a corrugated drain introduced through the presacral fascia into the presacral space behind the rectum. Drainage should be provided for an anastomosis performed under some difficulty and surrounded by loose cellular tissue, and this is best obtained through the space left after excision of the coccyx. The patient is then placed in the full Trendelenburg position and the initial stages of the usual abdomino-perineal operation are performed. Before ligating the vascular pedicle the blood supply of the sigmoid loop should be carefully examined, bearing in mind the length of the mesosigmoid and the distance to which it must reach. As a rule I have ligated between the sigmoid branches where there is a long and mobile sigmoid and below the last sigmoid branch where the bowel is short.

The effect of this ligation will become evident on the sigmoid colon while the rectum is mobilized. This is carried out to a low level, anteriorly from the vagina or pros-

rectum is divided, and two further sutures are inserted. These sutures serve to hold the rectal stump, to narrow the lumen of the rectal ampulla, which is larger than the sigmoid, and to prevent eversion. A point on the sigmoid with a good blood supply is selected, the mesosigmoid divided, and the sigmoid cut obliquely and anastomosed to the rectal stump (Fig. 3). Penicillin-sulphathiazole powder is sprayed around the anastomosis and the pelvis peritoneum is sutured over it and to the sigmoid colon.

The "Pull-through" Resection.—The essential features of this operation have been described. Its disadvantage is that a long sigmoid is of considerably more importance than in the preceding operation: its advantage, that it enables the surgeon to divide the bowel still closer to the ano-rectal ring. As an alternative to the "synchronous combined" position adopted by Lloyd-Davis

FIG. 3.—Four "stay" sutures are in position. Anastomosis with sigmoid has begun.

(1945), the abdominal part may be first completed, the patient being subsequently placed in the lithotomy position. As in the preceding operation, I prefer drainage through the coccygeal space with complete suture of the anastomosis. After both these operations the transverse colostomy will require closure. Two to four weeks appears to be a suitable interval if the anastomosis is sound. I do not believe a long delay to be either necessary or desirable in the majority of cases.

Results

The personal series here reviewed is of 86 consecutive cases of rectal and recto-sigmoid cancer operated upon since the war. Too small in number and too recent for any consideration of the end-results, they serve to show the frequency with which suitable cases may occur.

Abdomino-perineal or other combined operation	..	49
Abdominal resection and anastomosis	..	18
"Pull-through" resection and anastomosis	..	3
Abdominal resection (Hartmann)	..	1
Perineal resection (palliative)	..	1
Inoperable	..	14

Operability rate .. 84%

(Two patients upon whom resection was performed had small hepatic secondaries)

It will be seen that about one-third of the cases considered operable were found suitable for an anastomotic operation. I believe this percentage is too high: two of my cases should have had a combined operation. The abdomino-perineal is likely to remain the most common surgical attack against rectal cancer.

Complications.—Pelvic infection, fistula, stricture, and incontinence are the more serious complications which might follow these anastomotic operations. Necrosis of the rectal stump through interference with its blood supply has been described by Dixon. If the lateral ligaments of the rectum are fully divided the middle haemorrhoidal arteries must be severed and the rectal stump will depend mainly on the inferior haemorrhoidal arteries for its blood supply. These complications are less likely to occur and will be much less serious in their effects when the operation is performed on a non-functioning and "sterile" bowel. The last two patients upon whom I performed "resection-anastomosis" both developed fistulae. One of these was into the vagina, now happily healed, while the other was into the presacral space. These have been the only fistulae in this series.

FIG. 1.—Clamp and retractor applied. The proposed line of incision in anterior rectal wall is shown.

FIG. 2.—Anterior rectal wall divided. Two cobbler "stay" sutures are inserted.

tate, posteriorly, and laterally. A hysterectomy clamp, which takes up less room in the pelvis than any other, is applied 3 in. below the growth, and an assistant working from the perineum once more carefully swabs out that part of the rectum below the clamp. With the bowel on traction, the anterior wall of the rectum is now opened below the clamp (Fig. 1). Two cobbler "stay" sutures are inserted on each side (Fig. 2), the posterior wall of the

The healed anastomotic ring, easily palpable on rectal examination, is always smaller than the rectal ampulla, since it is the junction with the sigmoid. I have had several cases with a small anastomosis, but none have yet required dilatation with bougies. All anastomotic cases have been left with full control. There has been some rectal prolapse after the operation in two of my cases, and this complication has been noted by others.

Mortality.—There have been two deaths in this short series, in which 72 cases were submitted to some form of resection. Assuming a high operability rate, all operations for rectal cancer must carry a definite mortality, having regard to the age group of these patients. However, the mortality has altered very considerably during the past 20 years. Those who had the privilege of watching Miles perform his operation know that this is not due to any improvement in surgical technique but to the surgical aids and in particular to the sulphonamides and penicillin. The danger from sepsis, considerable in the past, is now small. The mortality rate of these operations should now be not more than 5%.

End-results.—The end-results of operations for rectal cancer which preserve a functioning anus have been discussed by Babcock, Bacon, Dixon, and others. d'Allaines,

after an exhaustive review of the published figures, concluded that the end-results were quite as favourable as those obtained by operations requiring a permanent colostomy. At the American Proctologic Society Meeting of 1947 Wangenstein (1948) described his results over a five-year period. He concluded that operations preserving the sphincter gave results equal to those obtained by the abdomino-perineal operation when the growth lay between 14 and 20 cm. from the anus, that the local recurrence rate in the surrounding pelvic tissues was too high to justify such operations for growths within 8 cm. from the anus, and that between 8 and 14 cm. the operation should be reserved for selected cases.

FIG. 4

Lloyd-Davies (1948) has recently described recurrences in "A" cases taking place at the suture line.

I have at present a patient upon whom I performed an abdominal resection and anastomosis for a high rectal growth two years ago. Examination of the operation specimen showed that an adequate length of bowel had been resected; all glands examined below the growth appeared free, but metastases were present in a gland at the highest level. This patient, a woman of 59, recently developed a polypoid carcinoma at the anastomotic site and a full abdomino-perineal resection has now been performed (Fig. 4). I am indebted to Dr. Cuthbert Dukes for the following report.

The specimen measured 11 in. (28 cm.) and consisted of a portion of the pelvic colon and the rectum. The line of

anastomosis from the original operation could be clearly seen about 3½ in. (8.75 cm.) above the ano-rectal line. There was a slight narrowing of the lumen in this region, but otherwise the mucosal surface looked normal except for a protuberant tumour half an inch (1.25 cm.) in diameter situated on the posterior quadrant. The tumour was attached to the mucous membrane by a broad pedicle, and from its general appearance it certainly seemed to be derived from the mucous membrane. In its gross characters the tumour appeared to be a pedunculated adenoma of doubtful malignancy. There was no evidence of extension into the adjacent perirectal tissues, which, however, were tough and fibrous.

Section shows the tumour to be an adenocarcinoma very well differentiated in character and, judged from its histology, of a relatively low grade of malignancy. There is evidence of spread to the submucous coat and slight invasion of the rectal muscle only. Sections cut through the thickened extra-rectal tissues show fibrosis and inflammatory infiltration but no sign of carcinoma. There was no sign of venous spread. Seven lymphatic glands were found and sectioned, but these were all free from metastases.

This is undoubtedly either a fresh primary tumour or the result of an implantation at the site of anastomosis of the previous operation.

If implantation is the cause of this type of recurrence it behoves the surgeon to exercise the greatest care in his technique, but it is a risk to which all bowel surgery for cancer must be exposed to some degree. By comparison I have two other patients who underwent an abdomino-perineal resection for rectal cancer within the past year and who have now developed fresh growths at and just above the terminal colostomy. These are surely examples of the inevitable and deadly trend of unhealthy and precancerous bowel. An abdomino-perineal operation will give increased protection against a further growth, but may not prevent it. Apart from the presence of obvious adenomata, our present knowledge does not allow us to predict when the retention of any rectal mucosa is fraught with any danger to a patient, though there are some who would say, "Always!"

Apart from the foregoing, it is germane to remind ourselves of several other points in the prognosis of rectal cancer. A high operability rate will almost certainly mean a reduced survival rate. It is known that if the lymphatic glands are not involved at the time of operation the prognosis is relatively good; in such cases the amount of bowel removed below the growth is not likely to affect the issue materially from this aspect. If at operation the glands are already involved the ultimate prognosis is less satisfactory, though considerably better with high removal of the lymphatic field than with a perineal resection. The operations which aim at the preservation of normal defaecation do remove the main lymphatic drainage system of the rectum to the same high level as an abdomino-perineal excision. If therefore a *judicious* selection of cases is made there is little reason why the results should not be comparable and a permanent colostomy be avoided in certain cases of rectal and recto-sigmoid cancer.

Conclusions

There is a sound pathological basis for operations which aim at preserving a functioning anus in high rectal and recto-sigmoid growths, but even in early cases and with adequate excision carcinoma can reappear at the anastomotic site.

To be certain of continence the ano-rectal ring must be preserved.

Of the various methods abdominal resection-anastomosis and a "pull-through" resection appear preferable.

A preliminary transverse colostomy lessens the risk and dangers of infection and should always be employed.

The use of sulphonamides and penicillin has reduced the mortality of all methods of rectal resection to a low figure.

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THE CLINICAL FEATURES OF MUSTARD-GAS POISONING IN MAN

BY

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The occurrence of general systemic symptoms following exposure to heavy dosages of mustard vapour or to massive liquid contamination was well recognized in the 1914-18 war. Since then experimental work on the subject has been largely concerned with the pathological changes observed in animals following the administration of mustard gas by different routes. These investigations have been reviewed by Smith (1943), who gives a comprehensive account of the literature.

In the absence of any large body of human experimental material, investigations on the changes in the haemopoietic system and blood chemistry of animals have tended to relegate to the background the clinical symptomatology produced in man by exposure to mustard gas. Isolated cases of accidental exposure have occurred from time to time, and some have been reported in the medical press (Hobbs, 1944). In these also, however, attention has been focused on the pathology rather than on the symptoms, many of which are nevertheless of the greatest importance, since their occurrence in the case of mustard-gas burns throws light on the mechanism by which similar symptoms arise following thermal burns.

It is difficult to demonstrate the occurrence of systemic manifestations in cases of slight or moderate mustard burns in temperate climates. In the Tropics, however, systemic poisoning by mustard gas is much more readily produced. From 1943 to 1945 I had the opportunity of observing a series of 438 volunteers exposed to mustard gas under tropical conditions, and thus of becoming familiar with the clinical picture of systemic mustard-gas poisoning.

Material and Methods

Of the 438 men observed 320 were exposed to mustard vapour and 118 to contamination by liquid mustard. In both the vapour and liquid groups the resultant burns were of all degrees of severity, ranging from a faint erythema of a localized area of skin to multiple ulcers many hundreds of square centimetres in area. All the men exposed to vapour and 77% of those exposed to liquid wore fully effective respirators throughout exposure.

The occurrence of systemic poisoning in these men was assessed both objectively, by daily clinical examination for a minimum period of 21 days after exposure, and subjectively, by daily interrogation. Each man was examined separately, and was asked only, "How are you feeling to-day in yourself?" No leading questions or suggestions were used.

Not all the symptoms of which the volunteers complained were easy to evaluate. Great care, however, was taken in each case to exclude adventitious causes, such as indulgence in the local mixture of lower alcohols, and to sort out genuine complaints from those which might be regarded as suspicious. In general, it was impossible to assign any accurate degree of severity to the subjective clinical symptoms owing to the variation in the general character and education of the volunteers. It is felt that considerable confidence can be placed in the findings, since they were recorded in men classified as A1 who were in good physical condition and well acclimatized to the Tropics. Further, the men had all volunteered to be exposed to mustard gas, and showed the keenest interest in the work.

Owing to lack of time and facilities it was only possible to follow blood changes in selected groups of men. The clinical pathology of some of the severely affected men was more extensively investigated.

Observations

Threshold and Severity

No symptoms attributable to systemic poisoning occurred in any vapour case in which no lesion more severe than erythema developed. There were 84 such men. Similarly, no man with liquid burns in whom the total raw surface ultimately produced was less than 20 square centimetres in area complained of systemic symptoms. In this category 83 men were included. Of the remaining 271 men, 102 reported one or more symptoms.

The severity of the effects varied within wide limits. In 35 men systemic manifestations were present on one day only, and in most of these cases the symptoms were in no way incapacitating. At the other extreme were cases in which systemic symptoms were a major factor in producing prolonged disability. In 37 men never more than one symptom was present, while the remaining 65 complained of two or more symptoms at various times. In general, the latter group included the more severely affected men.

Time Factors

Of the 102 men affected 66 (65%) showed symptoms within 24 hours of exposure; 83 (81%) were involved within 48 hours and 96 (94%) before the sixth day. It is also of interest that only 3 (16%) of the 19 cases in which the onset of symptoms occurred later than 48 hours after exposure could be described as more than very slightly affected. In contrast the onset of systemic symptoms in some of the worst cases preceded even the appearance of erythema of the skin.

Fig. 1 shows the number of men complaining of one or more systemic symptoms on each day after exposure. The number is largest on the first day, and falls fairly regularly till the end of the second week. No complaints were received from any man after the forty-fifth day. It is interesting that there is no correlation between the number of men complaining of systemic symptoms and the severity of the skin burns. Characteristically, the latter developed slowly, and in the vapour cases did not reach their maximal development until, on the average, 11 days after exposure. This time appeared to be independent of the severity of the lesions (Sinclair, unpublished work,