

will be little or no effect on the number of eosinophils. In aged patients who are "doing badly" in general after operation and seem to be "going to pieces," if the corticotropin test indicates poor function of the adrenal cortex substitution therapy in the form of administration of "cortisone" (adrenal cortical extract) has sometimes produced striking improvement in the patient's general condition. Therapy must be continued for some days or longer until the patient's general condition is good. At that time the dosage is very gradually cut down over the course of days so that the adrenal cortex will gradually be stimulated to resume functioning.

It is very important for the aged patient to get out of bed beginning the day after operation or even the afternoon after operation, if possible. This is done no matter what the operation was (unless the patient is in shock), and it is necessary to have plenty of assistance to help support the patient at first. It has been found that early

ambulation helps prevent postoperative complications, such as pneumonia, phlebothrombosis, and emboli. Psychologically these patients are tired and discouraged and need a lot of encouragement. Also, I have found that it does more harm than good to try too hard to change habits or customs of many years standing during the few weeks the patient is in the hospital, no matter how illogical or undesirable they may seem.

In conclusion, I would reiterate that the aged often present serious problems when undergoing surgery—urological or otherwise. However, despite these handicaps—with attention to their chronic diseases, nutrition, and water and electrolyte balance and aided by modern therapy, modern methods of anesthesia, and especially the liberal use of whole blood, the vast majority of these patients can be brought through major urological surgery satisfactorily.

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## INFILTRATING CARCINOMA OF THE BLADDER

### RELATION OF EARLY DIAGNOSIS TO FIVE-YEAR SURVIVAL RATE AFTER COMPLETE EXTIRPATION

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A recent study<sup>1</sup> of 80 cases of carcinoma of the urinary bladder was made in order to determine the influence of the depth of mural infiltration on the five-year results following complete extirpation of the primary growth. Thirty-nine patients subjected to simple cystectomy and 41 to segmental resection (partial cystectomy) prior to Feb. 1, 1946, survived operation. Of 19 patients with tumors infiltrating less than halfway through the muscularis, 14 (74%) lived 5 to 14 years without evidence of recurrence or metastasis, whereas only 2 of 61 patients (3%) with deeply invading tumors survived 5 years (Table 1). Moreover, only 10% of the patients with superficially infiltrating tumors died with evidence of extension of their vesical cancer, as compared with 85% of the patients with deep tumors.

The histologic pattern and degree of cellular differentiation of each tumor, although indicating the potentiality of that tumor for rapid growth and metastasis, were found to exert somewhat less influence on the survival rate than the extent to which the growth had invaded the bladder wall. However, it was pointed out that 54% of the deeply infiltrating tumors were highly malignant, as compared with 37% of the superficially infiltrating tumors. This was attributed to the fact that highly malignant tumors grow more rapidly and consequently are more likely to reach the deeper layers of the bladder wall before the diagnosis is made.

The present study, therefore, concerned the relation of early diagnosis to the depth of mural invasion and thus to the five-year survival rate after extirpation of the primary growth. Since the diagnosis, as a rule, is made only after cystoscopy, and cystoscopy is performed usually only after the onset of certain symptoms, the first objective was to determine the nature and duration of the symptoms which led to the diagnosis.

Of the original 80 patients on whom the previous report was based, 73 had symptoms attributable to the vesical neoplasm. Of the 7 patients eliminated from the series, two had urinary symptoms unrelated to their tumors; in one of these patients cystoscopy was performed because of a coincidental obstruction at the vesical neck and in the other because of a vesical diverticulum. In the remaining five cases the clinical history was not sufficiently detailed to permit inclusion.

The following series, therefore, consists of 14 cases with infiltration extending less than halfway through the muscularis, and 59 cases with infiltration extending halfway through or more. Hematuria and some form of vesical irritability (frequency, urgency, pain, burning on urination, or tenesmus) were the cardinal symptoms; these occurred singly or in combination in all cases (Table 2). In the total group of 73 cases gross hematuria was a complaint in 65; in 7 it was a terminal symptom and in 2 an initial symptom. In six additional cases microscopic hematuria was found on urinalysis, so that in 71 of 73 cases erythrocytes were present in the urine. Vesical irritability was a complaint in 55 cases, although infected urine was reported in only 17 and residual urine, averaging less than 2 oz. (60 cc.) in only 22. Four patients complained of difficulty of urination, three of pains in the rectum, hypogastrium, or bladder, and one of hematospermia, which probably was coincidental.

The histologic classification of the tumors included papillary, epidermoid, and undifferentiated carcinoma,

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adenocarcinoma, and mucus-forming adenocarcinoma. In the papillary and epidermoid groups well-differentiated, moderately differentiated, and poorly differentiated types were recognized.

In the accompanying chart the average duration of symptoms prior to operation has been determined for

TABLE 1.—Relation of Depth of Infiltration of Carcinoma of Bladder to Five-Year Survival Rate After Complete Extirpation

Depth of Infiltration	No. of Patients	No. Living 5-14 Yr. Without Tumor
Submucosal (Group A).....	14	10
Superficial muscular (Group B1) *.....	5	4
Total superficial infiltration.....	19	14
Deep muscular (Group B2) †.....	13	1
Perivesical (Group C).....	48	1
Total deep infiltration.....	61	2

\* Group B1 represents infiltration less than halfway through the muscularis.  
 † Group B2 represents infiltration halfway or more through the muscularis.

each type of tumor, and the results in cases with superficially infiltrating and with deeply infiltrating tumors are compared. Although the number of cases with superficially infiltrating tumors is too small to permit final conclusions, the curves of the duration of symptoms suggest that patients with deeply infiltrating tumors, for the most part, have symptoms for a considerably longer period than those with superficial tumors. In a larger series of cases it would be desirable to ascertain for each type of tumor the longest duration of symptoms compatible with infiltration less than halfway through the muscularis.

Furthermore, it should not be concluded from these curves that patients with deeply infiltrating tumors always have had their symptoms for a much longer period than patients with superficial tumors. These curves merely represent the average duration of symptoms, and in each histologic category there was at least one patient with a deeply infiltrating tumor whose symptoms had been present for a shorter period than is represented by the curve for the group with superficial tumors. More-

TABLE 2.—Incidence of Gross and Occult Hematuria and Vesical Irritability in Seventy-Three Cases of Infiltrating Carcinoma of Bladder

	No. of Cases	Hematuria		Vesical Irritability
		Gross	Occult	
With superficial infiltration	14	12 *	2	7
With deep infiltration.....	59	53 †	4	48
Total.....	73	65	6	55

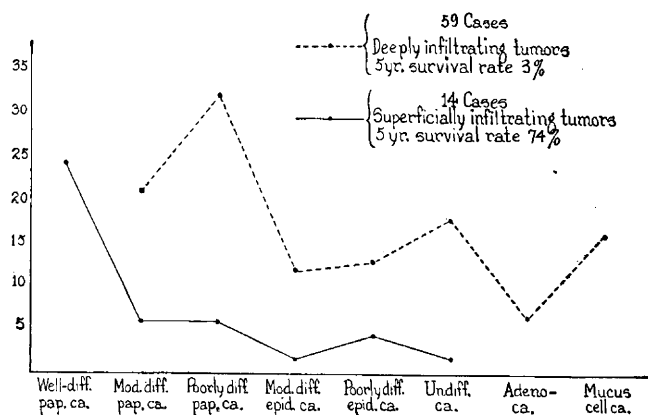
\* In three cases hematuria occurred at the end of urination, and in two cases at the beginning of urination.  
 † In four cases hematuria occurred at the end of urination.

over, two cases were eliminated from this series because the symptoms leading to cystoscopy were not attributable to the tumors, which were discovered accidentally.

The curves, however, seem to indicate that a patient with a deeply infiltrating tumor, although occasionally having no symptoms at all or symptoms of very short duration, generally will complain of hematuria or vesical irritability extending over several months. A patient whose symptoms have been present only for several

weeks is apt to have a superficial tumor. This, however, is less likely to be true in cases of epidermoid and undifferentiated carcinoma and adenocarcinoma. It should be borne in mind that the symptoms are not necessarily continuous. Their duration as recorded here is measured from the date of the first appearance of the symptoms, which may have disappeared promptly, only to recur a year or more later. This is especially true of hematuria, the degree of which is not a reliable indication of the magnitude of the tumor.

When the diagnosis is made late in the course of the disease, generally because significant symptoms have been disregarded for a period of time, the tumor usually will be deeply infiltrating. As previously pointed out, the five-year survival rate following simple cystectomy or segmental resection for tumors of this sort is about 3%. The more formidable procedures, such as radical cystectomy with resection of the lymphatic drainage area or perhaps pelvic exenteration, eventually may salvage a somewhat higher percentage of the cases in this group, but this is not certain since the survival rate with these procedures has not yet been determined. These operations furthermore may be found to result in a high



The average duration in months of symptoms from tumors of each cell type has been determined. Note the longer average duration of symptoms in the cases with deeply infiltrating tumors.

incidence of postoperative disability. At present little can be offered the patient with a deeply infiltrating tumor other than a certain degree of temporary palliation or an extensive pelvic dissection of unknown efficacy.

When the diagnosis is made early as the result of early occurrence of symptoms leading to prompt cystoscopic examination, the tumor in most instances, if infiltrating at all, will be superficial. The five-year survival rate in this superficially infiltrating group is 74% following complete extirpation of the local growth. This figure probably can be increased still more by improvement in technics, especially since only 10% of the patients in this group died with evidence of extension of the vesical cancer.

The reasonably good prognosis associated with superficial tumors, in contrast to the very poor prognosis afforded by deep tumors, should emphasize to the general public, the general practitioner, and the specialist the vital importance to the patient of immediate evaluation of the cause of hematuria or vesical irritability. In regard to the specialist, it is suggested that the treatment used be designed to result in immediate eradication of the

primary growth. This should be done either by complete local destruction or by extirpation so that superficial tumor cells will not be permitted to reach eventually the deeper layers of the bladder wall.

#### CONCLUSIONS

Often hematuria or vesical irritability of some degree makes its first appearance while the vesical tumor, if infiltrating at all, is still superficial. In such a case imme-

diately cystoscopic examination after the onset of these symptoms makes possible an early diagnosis. Complete extirpation of this superficially infiltrating tumor results in a five-year survival rate of 74%. Late or neglected symptoms or inadequate treatment after early diagnosis permit the inevitable infiltration of the tumor cells into the deep layers of the bladder wall, and complete extirpation then provides a five-year survival rate of only 3%.

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## UNRECOGNIZED PITUITARY NECROSIS (SHEEHAN'S SYNDROME)

### A CAUSE OF SUDDEN DEATH

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The clear relationship between a destructive lesion of the anterior portion of the hypophysis and the striking deficiency syndrome associated with it was first described by Simmonds, who attributed the ischemic necrosis to an infarct resulting from minute bacterial emboli lodging in the sinuses of the gland.<sup>1</sup> It was subsequently suggested by Reye that thrombosis of the small sinuses of the anterior lobe of the pituitary could result in necrosis, and that sudden hypotension would favor its occurrence.<sup>2</sup> He also pointed out that the enlarged pituitary of pregnancy and the hypotension resulting from severe postpartum hemorrhage would be an especially predisposing combination of circumstances for such thrombosis.<sup>3</sup> The latter suggestion was factually supported by the observations of several pathologists who noted the association of pituitary necrosis and postpartum hemorrhage.<sup>4</sup> However, the clinical importance of the relationship of postpartum hemorrhage to pituitary necrosis was not clearly understood until the revealing studies of Sheehan.<sup>5</sup> He not only reported the frequent occurrence of pituitary necrosis in women dying late in the puerperium after a difficult labor (one usually complicated by placental retention or postpartum hemorrhage) but he also demonstrated small thrombi in the sinuses of the anterior hypophysis.<sup>6</sup> Sheehan<sup>7</sup> believes that "at a normal delivery there is presumably a physiological reduction of the blood-flow to the anterior lobe; if in addition to this there is a severe general circulatory collapse, it is possible that the blood flow to the anterior lobe may be so reduced that thrombosis occurs in the vessels of the lobe and leads to ischaemic necrosis." Sheehan not only emphasizes the importance of severe postpartum hemorrhage in the pathogenesis of the ischemic necrosis, but also stresses the fact that this lesion is always associated with the end of a term pregnancy. There is as yet no recorded instance occurring during the course of a pregnancy. It is also interesting that in nonpregnant patients pituitary necrosis does not develop as a result of shock or hemorrhage, although it is occasionally encountered in diabetics.<sup>8</sup>

The necrosis of the anterior lobe of the pituitary following on postpartum hemorrhage develops slowly, re-

quiring approximately two weeks.<sup>9</sup> The fresh lesion is never the cause of an immediate postpartum death. The symptoms of such a necrosis do not appear in a clinical sense until at least six months have passed and may require several years to develop, depending on the degree of destruction of the gland. It has been shown experimentally that it requires destruction of at least 70% of the anterior lobe in order to evoke the typical pattern of chronic hypophysial deficiency.<sup>9</sup> There must, however, be a wide individual variation, because there are several reported instances of extensive pituitary necrosis found in patients at postmortem who had not suffered obvious symptoms of pituitary deficiency during life.<sup>10</sup> There is, nevertheless, a correlation between the symptomatology and the severity of the tissue destruction. The varying involvement of the three cell-types (basophil, acidophil,

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