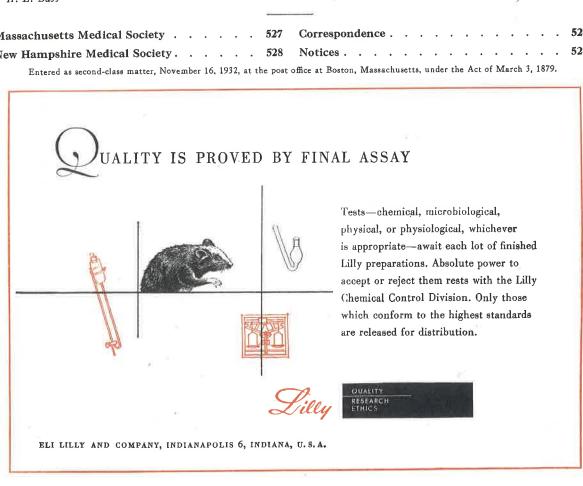
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Number 13

SURVIVAL IN PRIMARY CARCINOMA OF THE LUNG*

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THE ability to utilize a lung as a unit of excision has made it possible to think in terms of cure when that organ is the primary site of cancer. This state of affairs has existed but for fifteen years,1-4 and before that time cancer of the lung was invariably fatal. However new the experience in the surgical management of cancer in this location, a sufficient period has elapsed to permit a fair appraisal of benefits in respect to palliation and cure rates.

During the period in which surgery has been applied for carcinoma of the lung, one of us (R. H. O.) and his associates have examined a total of 604 patients in whom the diagnosis of primary carcinoma of the lung was made. This report is concerned with the ultimate fate of these patients. Survival periods in relation to clinical and operative findings, pathology and the extent of resection are given below. The factor of time between the onset of symptoms and the first request for help and the duration of the period of observation before reference for possible surgical treatment are considered. The necessity of setting ahead the time schedule of discovery by the use of screening methods is discussed.

The recent medical literature contains a number of comprehensive accounts that deal with incidence, symptoms and clinical manifestations of the disease, as well as with technical matters of lung excision. 5-8 The over-all problem of cancer of the lung has been particularly well presented by Churchill.9 A discussion of clinical features is not included in this report.

Material

From June, 1932, to August, 1948, a total of 604 patients in whom the diagnosis of primary carcinoma of the lung was made were seen. In 481 cases, the diagnosis was supported by microscopical proof. Great care has been taken to include only cases of carcinoma. Dr. Shields Warren and his associates have again reviewed the histologic sections and have excluded all cases of so-called "malignant" adenoma, adenoma, lymphoma and all secondary growths. In the unverified group no case was included in which there was reasonable doubt of the diagnosis. It is necessary to consider all cases seen if a true picture of operability and over-all salvage rates is to be obtained.

The sex incidence in this series parallels that in other reported groups. Of the verified cases, 85.8 per cent were in males and 14.2 per cent in females.

OPERABILITY

It has been our practice to advise surgical exploration in all suspected or proved cases with but

TABLE 1. Data in 604 Cases of Primary Carcinoma of the Lung (1932-1948).*

Operation	No. of Cases	No. of Deaths	
Exploration only	127	15 (11.8 %)	
Resection:	162	29 (17.9 %)	
Without extrapulmonary extension			
Totals	289	44 (15.2 %)	

^{*}Of these, 481 were verified.

two exceptions: absolute or strong presumptive evidence that the growth is out of bounds; and cases in which the patient's general condition is too pre-

TABLE 2. Data in 234 Cases of Primary Carcinoma of the Lung (1932-1943).*

Operation	No. of Cases	No. of Deathst
Exploration	58	9 (15.5 %)
Resection:	41	9 (21.9 %)
Without extrapulmonary extension 20 Lymph-node extension only		
	99	18 (18.1 %)
Totals	//	10 (1011 /0/

^{*}Of these, 190 were verified.

*Presented at the annual meeting of the New England Surgical Society, New Haven, Connecticut, October 1, 1948.

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carious or there are complicating factors such that there would not be a reasonable chance of success with either exploration or excision (Table 1).

[†]The five-year survival (4.3 per cent of all cases seen and 5.3 per cent of all verified cases) was distributed as follows: 8 cases without extrapulmonary extension and 2 cases with lymph-node extension only.

Of all cases, 48 per cent were explored, and resection was carried out in 27 per cent. In recent years, there has been an encouraging trend toward higher rates of operability, and in the past five years, 51 per cent of all cases seen have been explored and 32 per cent resected.

In Table 1 and 2 and Figure 2, 3 and 4 the resections are divided into three categories according to the extent of the lesion: patients with no demon-

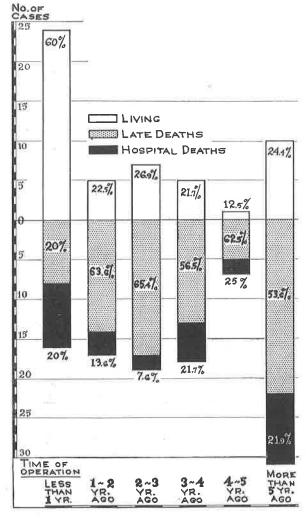


FIGURE 1. Survival in Total of 162 Patients who Submitted to Resection.

There were 29 operative deaths, 2 patients who could not be followed, 3 who died of causes other than recurrent cancer, and 2 epidermoid carcinomas that were not graded (leaving a total of 126 cases, which are considered in the succeeding figures).

strable extrapulmonary extension (these are the best candidates for cure); those with lymph-node metastases only, the regional lymph nodes being grossly involved in some and the metastases being found on microscopical examination in others (candidates for possible cure if the excised nodes represented the sole metastatic process); and those with gross evidence of extension, in turn divided into pa-

tients in whom all tumor was thought to have been removed (candidates for cure if all tumor is re-

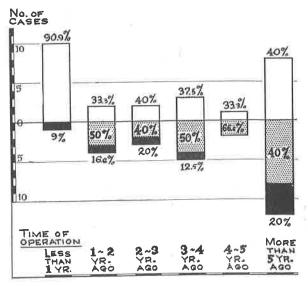


FIGURE 2. Survival after Resection in 56 Cases without Extension.

moved) and those in whom gross tumor was left behind (palliative procedure only).

SURVIVAL PERIODS

The survival periods of patients who were known to have died from their disease are shown in Table 3.

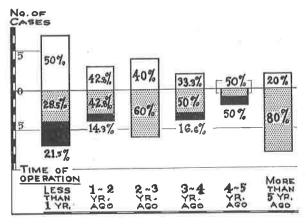


FIGURE 3. Survival after Resection in 49 Cases with Lymph-Node Extension Only.

In cases in which the cancer was obviously out of bounds and in which no surgical treatment was offered the patients lived an average of four and two-fifths months. At the other end was a group of 19 patients submitted to resection in whom the growth apparently was localized but who subsequently died of their disease. The average survival of this group was eleven and three-tenths months.

Figure 1 shows the survival periods of all patients who submitted to pulmonary resection. It will be seen that of the patients operated upon within the past year, 60 per cent are still alive, with 8 late deaths and 8 operative deaths. Of those operated upon five years or more ago, 24.4 per cent are still alive (10 patients).

An analysis of the survival periods in the cases without extension is shown in Figure 2. It will be seen that of 11 patients operated upon in the past year, there was 1 operative death, and all the rest are still living. Sixteen patients are living more than a year, 14 more than two years, 12 more than three years, 9 more than four years, and 8 more than five years after operation.

If operative deaths are excluded, 10 patients, or 100 per cent of those who survived operation within the past year, are still living, whereas 8 (50 per cent)

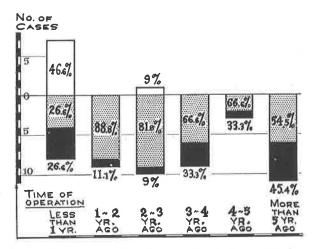


FIGURE 4. Survival after Resection in 58 Cases with Gross Extension.

of those who survived operation five or more years ago are still alive.

The average duration of life of those who died postoperatively (excluding hospital deaths) was eleven and one-tenth months. Of these, none lived longer than twenty-eight months.

Cases in which there was lymph-node extension only are shown in Figure 3. In the majority of these cases, the lymph nodes were found to be involved as a result of microscopical study, but in the few cases in which the glands were grossly involved, all tumor tissue was thought to have been removed. As can be seen from the chart, 8 of 28 patients are alive more than two years and 2 of 10 are alive five years or more after operation. Of the late deaths, the average duration of life was nine and three-fifths months. Of these, no patient lived longer than twenty-three months.

The group in which there was gross extension is shown in Figure 4. There were 34 cases in this group in which a palliative resection was done — that is, one in which gross tumor tissue was left behind. In the remaining 24 cases, gross extension was encountered, but all detectable tumor tissue was removed. This group includes the following: cases in which there was invasion of the ribs or chest wall; cases in which there was mediastinal invasion, including those in which there was invasion of the pericardium; and cases in which there was invasion of the diaphragm. In all, the invasion was apparent on gross examination, as distinguished from the lymphatic metastases of the preceding group.

Of 43 patients in this category operated upon more than a year ago, only 1 is alive. This man has an epidermoid carcinoma (Grade II) and has lived

TABLE 3. Survival Periods from Diagnosis to Death from Disease in Cases of Primary Carcinoma of the Lung.

TREATMENT	No. of Cases	Survival
		mo.
None	148	4.4
Exploration	102	7.0
Resection:		
Gross extension	33	10.0
Lymph nodes involved	22	9.6
No apparent extension	19	11.3

more than two years. His was a palliative resection in which gross tumor was left behind, so that there is no possibility of cure. All the other 7 survivors were operated upon less than a year ago. In this group, the average life of those who died postoperatively was ten months, excluding hospital deaths. The longest survivor lived twenty-nine months. This experience indicates that the prognosis is poor if gross extension has occurred, even if all detectable tumor is removed. We have been agreeably surprised at the number of survivors in the group with lymph-node extension. Other reports from the literature bearing upon this subject are few. Ochsner, DeBakey and Dixon8 reported that in their series of cases with either lymph-node or gross extension, only 2 of 27 patients in this combined group survived beyond a three-year period, and none beyond six years. Coleman¹⁰ reported the cures of 2 patients still living two and six years respectively after resection in which the tumor had invaded the ribs. In our own series there were 6 cases, but no patient has survived more than twentyseven months.

SURVIVAL IN RELATION TO TYPE OF PROCEDURE

The vast majority of patients in our resection series have been treated by pneumonectomy. Only by mass removal of the lung can all hilar lymph nodes be resected, and mediastinal dissection is facilitated. Occasionally, however, in a patient of advanced age or one with a narrow respiratory reserve who has a peripheral tumor, lobectomy may be preferable. This is particularly true if there is positive evidence of gross extrapulmonary extension. Palliative lobectomy was performed upon a few patients who had peripheral tumors with invasion of the chest wall that could not be totally resected. However, it has been found that these procedures are rarely satisfactory in relieving pain even if coupled with division of the intercostal nerves. Treatment by rhizotomy, high chordotomy or frontal lobotomy if the pain is severe should receive consideration. Lobectomy was performed on 8 patients in our series, 4 of whom were operated upon more than two years ago, and all these are dead. Four patients treated by lobectomy within the past two years are still living.

PATHOLOGY IN RELATION TO SURVIVAL

The pathological cell type is second only to the extension of the tumor in determining survival. The pathologist has divided all the pathologic cell types into three major classifications: undifferentiated carcinoma; carcinoma arising from glandular epithelium, including adenocarcinoma and carcinoma

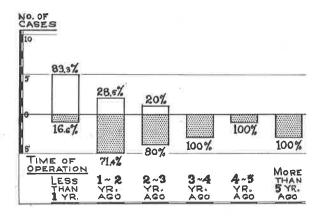


FIGURE 5. Survival after Resection in 25 Cases of Undifferentiated Carcinoma.

simplex; and epidermoid carcinoma, including subgroupings Grades I, II and III.

Only those who survived operation are considered. In the undifferentiated group (Fig. 5), there were 25 cases. There was no apparent extension of the tumor in 4 of the 7 patients operated upon more than three years ago, and yet none are living. In the late deaths, no patient lived longer than twentynine months, and the average duration of life of those who died was nine and three-tenths months.

In the adenocarcinoma group (Fig. 6), there were 12 cases. Of the 6 patients upon whom operation was performed more than three years previously, it will be seen that only 1 patient has survived. In this group of 6 cases, there were 3 without extension, 1

with lymph-node metastases only, and 2 with gross extension. The surviving patient had no demonstrable extension at the time of operation. The average duration of life of those who died was ten and two-tenths months, and of this group, none lived longer than twenty-seven months.

There were 10 cases in which carcinoma simplex was diagnosed (Fig. 7). None of the patients

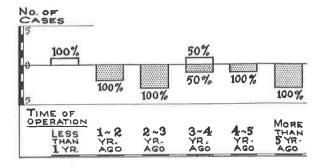


FIGURE 6. Survival after Resection in 12 Cases of Adenocarcinoma.

operated upon more than a year ago are still alive. Only 1 of 3 patients operated upon within the past year is still alive. In this entire group, there were 3 cases in which there was no apparent extension, 4 in which there was lymph-node metastasis only, and 3 in which there was gross extension. The average

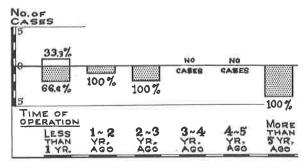


Figure 7. Survival after Resection in 10 Cases of Carcinoma Simplex.

duration of life of patients who died was seven and three-tenths months, and none lived longer than thirteen months.

The final group to be considered in relation of survival to pathological type is that in which the diagnosis was epidermoid carcinoma, and it is in these cases that the prognosis is most favorable.

In cases diagnosed as Grade I (Fig. 8) there were 10 cases. It will be seen that 4 of these patients are still living more than two years, 3 of 8 patients more than three years, and 2 of 5 patients more than ten years after operation. The 2 patients living more than five years after operation were both in the group

without apparent extension of any kind. The patients surviving for three and two years both had lymph-node metastases. Of those who died, 4 had gross extension, and 2 had lymph-node metastases; the average survival was fifteen and one-tenth

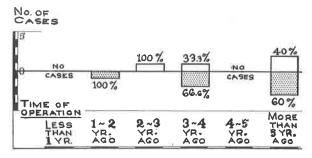


FIGURE 8. Survival after Resection in 10 Cases of Epidermoid Carcinoma (Grade I).

months, and yet no patient lived more than twentyseven months.

In the cases of epidermoid carcinoma (Grade II) there were 36 patients, of whom 20 still survive, 8 of 18 having lived longer than three years, and 5 of 10 having lived longer than five years (Fig. 9). In 3 of 5 cases in which there was no extension of

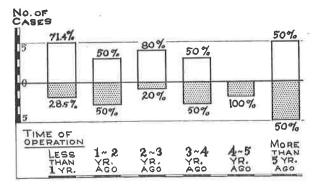


FIGURE 9. Survival after Resection in 36 Cases of Epidermoid Carcinoma (Grade II).

the tumor the patients have survived five years or more after operation, and 5 of 9 patients in this same group have survived three years or more. Two of 5 patients with lymph-node metastases are still living five years or more, and 3 of 8 cases are living three years or more after operation. No patient who died lived longer than twenty-four months, and the average survival was twelve and nine-tenths months.

Of 33 cases in the group diagnosed epidermoid carcinoma (Grade III), 3 of 6 patients operated upon five years or more ago and 4 of 8 operated upon more than four years ago still survive (Fig. 10). However, there are no survivors among the patients operated on three, two and one years

ago. Of those operated upon more than four years ago, the 4 survivors were in the group without extension of the tumor. In the intervening years, however, 3 other patients without extension have died. Four patients with lymph-node extension upon whom operation was performed more than a year ago have all died, as have 6 with gross extension. The average duration of life in the late deaths was eight and two-fifths months, and no patient lived longer than twenty-eight months.

SYMPTOMS AND SURVIVAL

All patients submitted to resection were divided into three groups: those who had symptoms for less

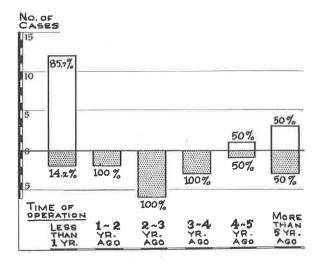


FIGURE 10. Survival after Resection in 33 Cases of Epidermoid Carcinoma (Grade III).

than six months; those with symptoms for six to twelve months; and those with symptoms for more than a year. One would expect to find a higher number of survivors in those patients who had symptoms for less than six months, and yet it was found that in this group the percentage of survivors was lower than that in patients who had symptoms for six to twelve months. The percentage of survivors of those who had symptoms for more than a year was about the same as that in patients who had symptoms for less than six months. This finding could be interpreted to mean that many growths are relatively far advanced by the time symptoms develop. No attempt was made, however, to correlate pathology with the duration of symptoms. Many patients with anaplastic tumors presented themselves before they had had symptoms for a year, whereas others with more slowly growing tumors waited longer before consulting a physician.

Those patients who survived for more than five years are shown in Table 4. All were treated by total pneumonectomy. Of these, 5 are well, 2 are reasonably well, and the last available information concerning another revealed that she was well in

1947. Of the 2 remaining patients, 1 was well for ten years but has gone downhill in the past two years and is now a respiratory invalid; the other was well for five years and has had a similar downhill course in the past two years. Both are apparently free of cancer but are suffering from a lack of respiratory reserve.

In the group of patients operated upon more than five years ago, there is an additional patient who died in an accident thirty-nine months after resection. He was working every day until his death, and was apparently free of disease. He prehistories of patients seen in 1947 and 1948 showed that the interval between the first symptom and the date of diagnosis had been reduced only to ten months. The average patient delayed seeing a doctor for three and eight-tenths months. The first x-ray film was ordered one and six-tenths months later, compared with an interval of three months in the earlier group. However, the diagnosis was not established until four and six-tenths months later.

The interval between onset of symptoms and diagnosis will have to be shortened; in fact, this

Table 4. Results in Patients Who Have Survived Five or More Years after Pulmonary Resection for Carcinoma of the Lung.

Case No.	DATE OF OPERATION	Age	Sex	Final Diagnosis	Present Status
		y_{τ} .	22		
7. 1	5 /13 /36	45	M	Epidermoid carcinoma (Grade II)	Patient well for 10 years; downhill in past 2 years; now respiratory invalid.
2	6/10/37	45	F	Epidermoid carcinoma (Grade III)	According to last information (1947), patient well
3	3 /18 /41	44	M	Epidermoid carcinoma (Grade III)	Patient well for 5 years; downhill in past 2 years; now respiratory invalid.
4	10/11/41	43	M	Epidermoid carcinoma (Grade I)	Patient well; does light work; some dyspnea upon exertion only.
5	5 /7 /42	56	M	Epidermoid carcinoma (Grade II)	Patient well
6	4 /16 /42	48	M	Epidermoid carcinoma (Grade II)	Patient well; works every day; some dyspnea upon exertion only.
7	7 /31 /42	48	M	Epidermoid carcinoma (Grade I)	Patient fairly well; does light work; tires easily.
8	8 / 28 / 42	54	M	Epidermoid carcinoma (Grade II)	Patient well
9	6/29/43	62	M	Epidermoid carcinoma (Grade II)	Patient well
10	7 /13 /43	55	M	Epidermoid carcinoma (Grade III)	Patient well

sumably had been cured, for in our entire series no patient who later died of his disease has lived longer than thirty months after diagnosis. This includes untreated patients, those in whom thoracotomy only was performed, and those who had pulmonary resection. All who died had signs and symptoms of cancer for several months prior to death, so that it appears from our experience that any patient who lives thirty months or more without symptoms of recurrence has an excellent chance for cure.

FUTURE POSSIBILITIES

The present method of waiting for symptoms, followed by the delay that seems to be necessary to work out the differential diagnosis, has not produced the results that we believe are possible in the present-day surgical treatment of primary carcinoma of the lung.

It was previously pointed out that an analysis of the histories of 133 patients seen between 1932 and 1942 revealed that there was an average interval of eleven and three-fourths months between the first symptom and the establishment of the diagnosis. The average patient delayed seeing a doctor for three months. The first x-ray examination was not ordered until another three months had elapsed. The diagnosis was established five and three-fourths months later. A review of the

interval can be eliminated altogether. The growth can be discovered before it is large enough to produce symptoms. Radiologic screening of the population, now being employed in uncovering cases of silent tuberculosis, can be further extended. Older age groups should be included, and the screening should be repeated each year. Early carcinomas usually produce changes in the x-ray picture that can be detected by the experienced observer, even if the tumor itself will not cast a shadow. Approximately 80 per cent of the lesions are situated in a lobar or segmental bronchus, and the secondary changes in the corresponding segment or lobe, incident to partial or total bronchial occlusion, cast abnormal shadows detectable in the miniature film used for screening. There is a period during the growth of the tumor when abnormal x-ray densities develop and then symptoms appear. Part of this period of silent growth can be saved. The minority group of peripheral tumors cast direct shadows, which, even in their early stages, should be caught in the screening process owing to the highly rarefied normal lung field. If abnormal densities are discovered, they will require proper identification without delay. Additional x-ray studies should be arranged for immediately. Cytologic examination of the sputum and of material aspirated from the bronchi (Papanicolaou technic),

bronchoscopy or even exploratory thoracotomy may be necessary to settle the diagnosis.

Efforts to discover primary carcinoma of the lung in its silent and early stage will be rewarded. The risk of resection is reasonably low and is constantly being lowered. Five-year survival rates for patients treated at a time when the growth was apparently localized have been high.

SUMMARY

Statistics bearing upon operability and survival of 604 patients in whom the diagnosis of primary carcinoma of the lung was made are presented.

The extension or localization of the lesion and the pathological cell type are the most important factors in survival after resection.

With known and available methods of screening for silent lesions, a significant increase in the salvage rate in primary cancer of the lung should be possible.

In the identical period of the above study (1932-1948), 27 patients were treated by pulmonary resections for tumors diagnosed as bronchial adenoma, infiltrative bronchial adenoma or malignant adenoma. Some authors consider these tumors to be primary carcinomas (adenocarcinoma, Grade I) and include them in their cancer statistics. From a clinical point of view, they should receive special considera-tion. For example, 26 of 27 patients have been followed re-cently, and there has been only I late death. This patient died of a metastasis that had similar characteristics to the

bronchial tumor. One patient has not been followed. Ten of the remaining 25 patients have lived five to fifteen and a half years after operation. In the adenoma series, there were no operative deaths; therefore, since immediate and late results are so totally different in the "so-called" adenoma group, we have not included them in the above paper on true cancer of the lung.

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PULMONARY EMBOLISM*

Analysis of 74 Autopsy Cases Since 1941

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BOSTON

THERE has been no significant decrease in the percentage of cases in which pulmonary emboli were demonstrated at autopsy at this hospital group since the introduction of definitive and prophylactic treatment of venous thrombosis. therapy includes venous interruption and the administration of heparin and dicumarol, as well as prophylactic exercises, early ambulation and even paravertebral autonomic block in one case. During the thirteen years from 1928 through 1940 pulmonary emboli were found in 7.5 per cent of all autopsies, whereas the figure became 6.7 per cent during the following six-year period (Table 1). The percentage of operations that were followed by pulmonary embolism, as found at post-mortem examination, has decreased somewhat more in the same intervals. Before January, 1941, the figure was 0.13 per cent; since that date it has dropped to 0.09

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per cent, but even this decrease is not definitely significant statistically.

Because there are so many factors that may change over a period of years, making statistical data questionable, Table 2 was compiled. It shows the various relations between the number of hospital admissions, operations, deaths, autopsies and pulmonary-embolism autopsies per year since 1928. The ratio of operations to hospital admissions has gradually increased over the years. We feel safe in concluding that the other individual ratios have not changed enough to make the above percentages on pulmonary embolism at autopsy lose their significance.

The standard error of the difference for the percentages was calculated according to the formula given in Arkin and Coiton. The actual difference between the two figures (7.475-6.685=0.790) is only 0.22 times the standard error of the difference (3.584). This is definitely not significant, for the chances are more than eight out of ten that the actual difference is an accidental one.

Using the same formula for the percentage of operations followed by embolism as that found at autopsy for the same groups of years, we find that the actual difference between the two (0.0412 per cent) is 2.3 times the standard error of the difference (0.0177 per cent), which may be significant.

Dr. Darling, the new co-ordinator, a graduate of Harvard Medical School, served as assistant director of the Fatigue Laboratory at Harvard and also as a consultant to the Quartermaster General. His studies have particularly dealt with various aspects of physical fitness, and he recently rendered a report on this subject in the Journal of the American Medical Association as chairman of the Baruch subcommittee on physical fitness. The organization of such a strong program in physical medicine at Columbia should attract competent young physicians into this rapidly growing and important field of medicine.

CANCER OF THE LUNG

Overholt and Schmidt, in their paper on survival in primary carcinoma of the lung, delivered at the annual meeting of the New England Surgical Society last October and published elsewhere in this issue of the *Journal*, have made a valuable contribution to the increasing knowledge of cancer.

Improvement in the operability rates and in the operative results are encouraging but are to be expected, particularly in a branch of surgery that has been so recently developed as has been surgery of the lung. Less encouraging and presenting, indeed, a distinct challenge to both medical practice and medical public relations is the time that still elapses between the first symptom experienced by the patient and the establishment of the diagnosis.

This tragic interlude averaged eleven and three-fourths months for 133 patients who were seen between 1932 and 1942. Three months elapsed before the patient visited the doctor, another three months passed by before the first x-ray examination was made, and still another five and three-fourths months were lost before the diagnosis was made. Since 1942 this long interval has been reduced only to ten months. The doctor is now not consulted for three and eight-tenths months, the first x-ray examination is made one and six-tenths months later, and four and six-tenths more precious months elapse before the diagnosis is established.

This total interval can, conceivably, be completely eliminated by the same type of radiologic screening of the population that is now employed in tuberculosis case finding, for the growth can usually be discovered by the experienced radiologist or chest specialist before it begins to produce symptoms. Notice of abnormal areas of density spotted in survey films is reported back to the referring physician. It is his responsibility to see that any silent, abnormal density is properly labeled. His patient may have a silent, primary cancer of the lung, which, in most cases, is localized and can be treated successfully then, but not later.

Cancer of the lung should carry the highest rates of cure of any type of internal cancer because the time schedule of discovery can be set ahead to antedate symptoms. The responsibility is threefold: support by the laity of mass screening of the adult population on an annual basis; proper sorting of areas of silent abnormal densities by the medical profession generally; and reliance on exploratory thoracotomy in suspected cases.

UNWISE DRAFT DEFERMENT

According to a recent release from the University News Office, the Faculty of Medicine of Harvard University has decided to continue its present policy of certifying for Selective Service deferment only students who are eligible to enter medical or dental school in the fall of the current year. Under the provisions of Local Board Memorandum No. 7 of National Headquarters, Selective Service System, the faculty was empowered to certify men in their first and second years of college by regarding them as premedical students and by provisionally recording their names for admission to future medical studies. The refusal to avail itself of this power represents a wise and honest decision on the part of the Harvard faculty.

A similar decision has been reached by a few other outstanding schools, notably, Boston University, University of Cincinnati, Johns Hopkins, University of Missouri, University of Wisconsin and Yale, but the remaining medical faculties throughout the country are still undecided. The dilemma confronting them is more important than it seems at first sight.

The folly of allowing military service to cut off the supply of future doctors, even in time of war, was