whose lung function is already impaired is more likely to cause respiratory insufficiency in the immediate post-operative period. It is suggested that any such patient should have the pulmonary function assessed before operation so that measures may be taken to combat any post-operative anoxia which may arise.

Summary

Measurements of the total lung capacity and its subdivisions were made on 26 male patients.

Significant reductions occurred in the total lung capacity, inspiratory capacity, expiratory reserve volume, vital capacity, and functional residual capacity after abdominal operations, and these changes were more marked after those on the upper abdomen.

Possible causes of these changes are briefly considered.

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OPEN HEALING OF TUBERCULOUS CAVITIES

RESULTS IN 40 PATIENTS TREATED CONSERVATIVELY

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With the development of rational chemotherapy the phenomenon of open-cavity healing in pulmonary tuberculosis is becoming increasingly evident. From the extensive literature on the subject a few observations are summarized.

Auerbach and Small (1957) state: "For practical purposes it is the opinion of the writers that those cases should be accepted as open healing in which the lumen of the cavity is free of necrotic contents, the inner aspect contains no pyogenic membrane or necrotic lining, and the cavity wall contains no necrotic foci." The same writers comment that, although open healed cavities often appear cystic, the radiological appearances are deceptive in that a thin-walled cavity may present evidence of active disease and a thick-walled cavity may be healed. They believe that open-cavity healing is less common than might be supposed and point out that, despite the absence of tubercle bacilli from the sputum for many months, a resected cavity may show the

presence of a necrotic lining. They admit, however, the increasing frequency of open healing after long-term chemotherapy and suggest that where the sputum has been negative for tubercle bacilli for more than seven months four out of five cyst-like cavities prove to be instances of open healing. In their experience isoniazid has not significantly increased the incidence of healing.

Corpe and Stergus (1957), on the other hand, believe that isoniazid is of great importance in this connexion. In their cases open healing was observed to occur most often when a triple-drug regime of streptomycin, P.A.S., and isoniazid had been used. They are not sanguine about the conservative management of such cavities, and state: "The possibilities of rupture, suppuration, haemorrhage, and reactivation of tuberculosis are well recognized. Accordingly, it is believed that when these openly healed or healing cavities are unilateral, or bilateral, they should be excised if the patient is otherwise fit for surgery." A similar opinion has been expressed by Chenebault (1954). Caffey (1950) explains the pathogenesis of pulmonary cysts during respiratory infections. Such cysts may develop during the course of treatment and may be indistinguishable radiologically from thin-walled cavities. Auerbach (1955) states: "After chemotherapy such healed cavities may be mistaken for lung cysts or emphysematous blebs. It is believed that such areas may be accepted as open healed cavities if they occupy the site of a cavity visualized in the roentgenograms, if bronchi communicate with them and if they do not surround an inspissated cavity or radial scar."

Most papers on the subject are concerned with the pathological findings in resection specimens. Little is known of the fate of patients who continue to receive drug therapy alone without resection therapy after they have achieved presumptive open healing of tuberculous cavities. Douglas and Horne (1956) have reported on six such patients. Corpe and Stergus (1957) indicate that they are in the process of making such a study. Raleigh and his co-workers (Raleigh 1957; Bell, Decker, and Raleigh, 1957) have reported unfavourably on the conservative treatment of patients in this category.

This paper records our own experience with indefinitely prolonged chemotherapy in 40 cases of advanced pulmonary tuberculosis with persistent cavitation. The cases recorded are the most grossly diseased of a large series of patients treated by prolonged chemotherapy in this unit over the past five years. They have been observed for periods ranging from one and a half to five years. The distribution of the patients is shown in Table I. Twenty-nine patients have been observed for more than two years and 17 for more than three years.

TABLE I.—*Distribution of 40 Cases Observed for One and a Half to Five Years*

	Period of Observation in Years				
	>5	4-5	3-4	2-3	1-2
No. of patients starting treatment	2	4	11	12	11
Total No. of patients under observation	2	6	17	29	40

Methods and Materials

By virtue of age, advanced disease, or poor respiratory function 37 of the patients were judged unsuitable for surgical treatment. A further three refused surgery. All were sputum-positive at the beginning of the study, the finding of a positive culture for *Mycobacterium tuberculosis* being considered obligatory to their inclusion in the

series. Thirty-five had received no previous treatment and five had had previous chemotherapy with drug combinations considered unlikely to produce drug-resistant organisms. In every case the organisms were fully sensitive to streptomycin, P.A.S., and isoniazid, as judged by the standard M.R.C. techniques. Cavitation, the total diameter of which was not less than 5 cm., was present in every case.

All were treated in hospital for periods ranging between 4 and 35 months, the average duration of stay being 14 months.

Thirty-two of the patients received a triple-drug regimen for at least the first year of treatment—streptomycin (usually streptoduocin), 1 g. daily, intramuscularly with P.A.S. (sodium salt), 10 g. daily, and isoniazid, 0.2 g. daily, by mouth in two divided doses. Triple-drug therapy was thereafter continued until resumption of employment or other circumstances made it difficult to arrange the administration of streptomycin. Eight patients received varying drug combinations for reasons stated in Table II. Particular care was taken to "sell" long-term chemotherapy to each patient. At each visit to the chest clinic patients were questioned in detail about the drugs they were taking;

TABLE II.—Cases Receiving Drug Combinations Other than SPH for a Minimum Period of One Year

Case No.	Drugs Employed	Reason
13 36	S ₂ H SH 12/12→S ₂ H	} Unable to tolerate P.A.S.
21 20	SH SPH 6/12→SH	
28	SPH 8/12→10 PH	Partial nerve deafness
7 15 16	S ₂ H 24/12→10 PH SP 12/12→SH 1/12→10 PH SH 13/12→10 PH	} Failure to receive standard combination was oversight

SPH=Streptomycin 1 g., P.A.S. 10 g., isoniazid 0.2 g. daily.
S₂PH=Streptomycin 1 g. thrice weekly, with P.A.S. 10 g. daily, and isoniazid 0.2 g. daily.

SH=Streptomycin 1 g. daily with isoniazid 0.2 g. daily.
S₂H=Streptomycin 1 g. thrice weekly with isoniazid 0.2 g. daily.
10 PH=P.A.S. 10 g. daily, isoniazid 0.2 g. daily.

they were invited to discuss any difficulties they might have with chemotherapy, and were repeatedly encouraged and advised about the security afforded by careful adherence to the prescribed regimen. All of the patients, except one, continue to take antituberculosis drugs. This individual (Case 4) passed to the care of another physician, who stopped the drugs after 30 months' continuous chemotherapy. In hospital chest x-ray films were taken every six weeks; out-patients were x-rayed at intervals of not more than three months. Tomograms were taken roughly at the end of each year of treatment. (In any instance where the persistence of cavitation was uncertain, tomograms have been taken during the past two months. In this connexion it should be recorded that there were originally 60 patients in the series, of whom 20 were discarded because of failure to demonstrate beyond any doubt the persistence of cavitation. No patient was withdrawn from the series for any other reason.)

The sputum of in-patients was examined each month by smear and culture, and sensitivity tests were carried out on all positive cultures. For out-patients the sputum was similarly examined on three consecutive days each three months. At the end of each year of treatment all antituberculous drugs were withheld for a period of four weeks. During the fourth week daily specimens of sputum, or a series of laryngeal swabs, were obtained.

Results

A detailed list of patients is given in Table III. All showed marked clinical and radiological improvement, which usually continued into the second or third year of treatment. Tomograms taken during the second and third years of treatment showed marked resolution of disease: in all instances the appearances did not suggest the persistence of large residual necrotic foci. Multiple cavities persisted in 28 patients; the remainder had solitary residual cavities. Twenty-five patients had thin-walled cyst-like

TABLE III.—Summary of Cases

Case No.	Date of Beginning of Treatment	Chemotherapy		Time Taken in Months for Sputum Conversion	Residual Cavitation		Total Diameter (cm.)
		SPH	Other Combinations		Site	Radiological Appearance	
1	17/11/52	16/12	→S ₂ PH 3/12→S ₂ H 18/12→10 PH	6	L.U.L. (S)	Cystic	2.5
2	15/1/53	15/12	→S ₂ PH 14/12→10 PH	15	R.U.L.; L.U.L.	R.U.L., multiple thick-walled cavities; L.U.L., cystic	25
3	19/6/53	12/12	→S ₂ PH 12/12→10 PH	9	R.U.L.; L.U.L.	Cystic	5
4	20/7/53	12/12	→10 PH 18/12*	4	R.U.L.; R.L.L.	"	7
5	3/9/53	18/12	→SH 9/12→10 PH	5	R.U.L. (S)	"	5
6	24/2/54	12/12	→S ₂ PH	7	R.U.L.	Thick-walled	8
7	7/7/54	Nil	S ₂ H 24/12→10 PH	3	R.U.L.; R.L.L.	Cystic	8
8	8/7/54	12/12	→10 PH	1	R.U.L. (S)	Thick-walled	2.5
9	11/9/54	19/12	→10 PH	2	R.U.L.	Cystic	12
10	6/10/54	12/12	→S ₂ PH	1	R.U.L.; L.U.L.	"	15
11	18/10/54	24/12	→10 PH	4	R.U.L.; L.U.L.	R.U.L., thick-walled; L.U.L., cystic	15
12	27/10/54	12/12	→S ₂ PH 6/12→10 PH	2	R.U.L. (S)	Thick-walled	2
13	1/11/54	Nil	S ₂ H	1	R.U.L. (S)	"	3
14	1/11/54	12/12	→10 PH	1	R.U.L. (S)	"	6
15	1/11/54	Nil	SP 12/12→SH 1/12→10 PH	2	R.U.L.; L.U.L.	Cystic	5
16	1/11/54	Nil	SH 13/12→10 PH	1	L.U.L. (S)	"	3
17	15/1/55	27/12	→10 PH	2	R.U.L.; L.U.L.	"	4
18	30/3/55	32/12†	→10 PH	1	R.U.L.; L.U.L.; L.L.L.	"	18
19	26/4/55	12/12	→10 PH	1	R.U.L.; L.U.L.	Thick-walled	14
20	1/6/55	6/12	→SH	1	R.U.L. (S)	"	4
21	1/7/55	Nil	SH	4	L.U.L. (S)	Cystic	7
22	3/7/55	18/12	→10 PH	1	L.U.L. (S)	Thick-walled	6
23	3/7/55	29/12†	→10 PH	4	L.U.L. (S)	Cystic	7
24	5/7/55	14/12	→S ₂ PH	1	R.U.L.	Thick-walled	8
25	16/7/55	17/12	→10 PH	1	R.U.L. (S)	"	6
26	27/7/55	29/12†	→10 PH	1	R.U.L.	"	12
27	3/9/55	21/12	→S ₂ PH	1	R.U.L.; L.U.L.	Cystic	10
28	1/10/55	8/12	→10 PH	1	R.U.L.; R.L.L.; L.U.L.	R.U.L. and R.L.L. thick-walled; L.U.L. cystic	12
29	2/10/55	17/12	→10 PH	4	R.U.L.; R.L.L.; L.U.L.; L.L.L.	Cystic	25
30	16/1/56	12/12	→10 PH	2	R.U.L.; R.L.L.	"	8
31	16/3/56	12/12	→10 PH	1	R.U.L.; L.U.L.	"	8
32	20/4/56	15/12	→10 PH	2	R.U.L.; L.U.L.	"	6
33	23/4/56	13/12	→S ₂ PH	1	L.U.L.	"	2
34	1/5/56	15/12	→S ₂ PH	3	R.U.L.; L.U.L.	"	7
35	7/5/56	12/12	→S ₂ PH	1	L.U.L.	Thick-walled	4
36	1/5/56	Nil	SH 12/12→S ₂ H	1	L.U.L.	Cystic	6
37	6/6/56	30/12†	→10 PH	1	R.U.L.; L.U.L.	"	6
38	6/9/56	27/12†	→10 PH	1	R.U.L.; L.U.L.	"	12
39	1/10/56	12/12	→S ₂ PH	2	R.U.L.	"	3
40	3/10/56	14/12†	→S ₂ PH	6	R.U.L.; L.U.L.	"	10

* = Chemotherapy discontinued. † = Daily SPH continued. (S) = Single cavity present.
S₂PH = Streptomycin 1 g. twice weekly, with P.A.S. 10 g. daily, and isoniazid 0.2 g. daily.

cavities; in 12 the residual cavities were apparently thick-walled; and in 3 both varieties persisted.

The rate of sputum conversion is indicated in Table IV. In most instances this was rapid, 37 patients becoming sputum-negative within six months. Of the remainder, two

TABLE IV.—Rate of Sputum Conversion

Months of observation:	0	1	2	3	4	5	6	7	9	15
No. sputum-positive	40	20	13	11	6	5	3	2	1	0
% sputum-positive	100	50	32.5	27.5	15	12.5	7.5	5	2.5	0
No. sputum-negative	0	20	27	29	34	35	37	38	39	40
% sputum-negative	0	50	66.5	72.5	85	87.5	92.5	95	97.5	100

Average time for sputum conversion, 2.7 months.

became negative during the seventh and ninth months respectively. The last patient remained intermittently positive for 15 months. In this patient (Case 2) the last positive culture was obtained two months after the start of treatment. During the ensuing 13 months the sputum was positive on direct smear on four occasions, but no growth was obtained on culture. One patient (Case 9) produced a solitary positive sputum culture during the third year of observation. The organisms cultured were fully sensitive to streptomycin and P.A.S. and partially resistant to isoniazid. Eight subsequent examinations were negative. The remaining 39 cases remained consistently sputum-negative after conversion.

Apart from the instances listed in Table II, prolonged chemotherapy presented few problems. Two patients became allergic to streptomycin, the first (Case 30) after one year's treatment and the second (Case 11) after two years' continuous therapy. Table V shows that the majority were fit enough to return to work. With two exceptions the patients remained well during the period of observation. During the fourth month of treatment Case 29 developed

TABLE V.—Indicating Number of Patients at Work and Incidence of Late Complications

Years of observation:	<1	1-2	2-3	3-4	4-5	5-6
Total No. of patients ..	40	40	29	17	6	2
No. at work ..	2	8	24	14	4	2.
Complications ..	1*	Nil	Nil	Nil	1†	1†

* Case 29. † Case 2.

multiple tension cysts, which subsided spontaneously (Figs. 1, 2, and 3). During the fourth year of treatment Case 2 developed repeated episodes of secondary infection in a cavitated right upper lobe. (This patient has deteriorated both clinically and radiologically, and has developed hypertrophic osteoarthropathy. Right upper lobe resection is being arranged.)

Discussion

The results of treatment in this incomplete investigation, although inconclusive, are none the less gratifying. They do not support Raleigh's (1957) adverse findings: this, however, is not surprising, as his patients received insufficient chemotherapy for his observations to be valid. It is clear that with adequate chemotherapy even the most

FIG. 2.—Case 29. Radiograph, showing multiple tension cysts, taken at four months of treatment.

FIG. 1.—Case 29. Radiograph taken before treatment.

FIG. 3.—Case 29. Radiograph showing spontaneous subsidence of cysts.

extensive disease can be controlled and rendered non-infectious. The findings support the claim of Corpe and Stergus (1957) that a triple-drug regimen of streptomycin, P.A.S., and isoniazid is the most effective drug combination in present use. There is as yet no statistical proof of this contention, but it is perhaps significant that the results obtained in the present series, using daily streptomycin, P.A.S., and isoniazid, are superior to those reported where only two drugs were used in combination. This aspect will be discussed in a subsequent communication. The fact that little difficulty was encountered with long-term chemotherapy is probably due to a number of factors. Firstly, the patients were well indoctrinated while in hospital. Secondly, they have remained under the care of the same medical attendants throughout their treatment. Thirdly, throughout their treatment the patients have been constantly reminded of the necessity to take the drugs prescribed. Lastly, but by no means least, general practitioners have than co-operated admirably in the supervision of chemotherapy.

Two striking features in the patients observed have been the rapid disappearance of tubercle bacilli from the sputum and the degree of resolution of pulmonary disease as judged radiologically by the apparent absence of large residual necrotic foci. The findings suggest that, where prompt sputum conversion is associated with considerable resolution of disease with apparent absence of large residual necrotic foci, the persistence of pulmonary cavitation need not present an indication for surgical treatment provided adequate chemotherapy has been employed from the beginning of treatment, accompanied by careful bacteriological control.

How long should chemotherapy be maintained? This problem remains unsolved. The available evidence suggests that two years is the minimum effective period. Our experience of chemotherapy is of not less than three years' duration. In view of the advanced disease of the cases in this series it has been decided to administer drugs for a minimum period of five years. Since secondary infection occurring in only one patient is the only serious complication that has been encountered here, the reported hazards in persistent cavitation of rupture, suppuration, haemorrhage, and reactivation of tuberculosis must be accepted with some reserve. At the same time it must be stressed that the patients have been followed up for only a short period. There is plenty of time for the development of late complications.

Summary

The phenomenon of open healing of tuberculous pulmonary cavities is briefly described.

A study is presented of 40 patients with advanced pulmonary tuberculosis treated by means of prolonged chemotherapy who remained sputum-negative despite the persistence of cavitation. The patients were followed up for periods ranging from one and a half to five years.

Success of the treatment is attributed to the use of a triple-drug regimen of daily streptomycin, P.A.S., and isoniazid. In certain cases the persistence of pulmonary cavitation need not necessitate surgical treatment.

Secondary infection in a cavitated lobe in one patient was the only late complication observed.

We are grateful to Dr. K. V. Lodge, and to her staff in the department of pathology at Baguley Hospital, for carrying out the bacteriological investigations of the patients in this series.

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DISTURBED CHRONIC PSYCHOTIC PATIENTS: PILOT TRIAL OF "STELAZINE"

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In the search for a more efficacious drug with which to treat long-stay psychotic patients in hospital, "stelazine" (SKK5019; trifluoroperazine) was given a trial. In the U.S.A. it had been described as having nine times the potency of chlorpromazine in blocking conditioned response. Its specificity was also stated to be greater than that of chlorpromazine. Jaundice had not been seen, but extrapyramidal signs and symptoms as in Parkinsonism had been described. Other side-effects noted included rashes, dizziness, drowsiness, lactation, lacrimation, and, on occasion, anxiety.

Method

Twenty-five female chronic psychotic patients who were extremely disturbed in behaviour unless treated with tranquillizing drugs or E.C.T. were chosen. All except three voluntary patients were detained under certificate. The duration of illness ranged from 5 to 31 years, and the average length of stay in hospital was 13 years. Twenty-three were chronic schizophrenics, of whom eight had been leucotomized, and two were oligophrenics with psychosis. In the past, 10 had had deep I.S.T. and 24 E.C.T. more recently.

All other treatment was suspended during the trial. The dosage of stelazine was built up gradually over a period of two weeks to 30 mg. daily, and in one case to 40 mg. and in another to 45 mg. daily. Treatment lasted four weeks, and the dosage was reduced gradually in discontinuing the drug.

Benzhexol hydrochloride, 6-8 mg. daily, was used to counteract side-effects.

Side-effects. (see Table).—These were pronounced and consisted chiefly of the Parkinsonian syndrome. Only seven patients did not seem to suffer from this, but one of them complained of feeling unsteady. Benzhexol was effective in decreasing the salivation but had little effect on tremor. On one occasion a patient had a pyrexia of 101° F. (38.3° C.) which persisted at 99° F. (37.2° C.) for several days until the dose was reduced. Twelve patients needed to be nursed in bed and five required feeding and full nursing attention. These patients were a constant source of worry to the nursing staff in preventing them falling out of bed or otherwise hurting themselves by their restlessness. After discontinuance of the drug these effects were apparent for more than a week, although subsiding gradually.

	Side-effects	No. of Patients
Masklike facies		6
Tremor		12
Salivation		7
Rigidity		7
Flushing		3
Pallor		2
Restlessness		13
Nursed in bed		12
Needed feeding and full nursing attention		5

Loss of weight was noted in 18 cases. One patient had lost 14 lb. (6.4 kg.) (as she was obese, this was acceptable) and two patients lost 7 lb. (3.2 kg.). Seven patients had gained moderately.

The changes in behaviour were: very slightly improved, 6; no change, 10; worse, 6; and much worse, 3.

The improvement that occurred in six cases was marred by side-effects in all but two. The little progress made could have been obtained by other means without such untoward