CORTISONE IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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THE treatment of pulmonary tuberculosis by cortisone combined with standard chemotherapy is the subject of this preliminary report. Since Hench (1949) first reported its beneficial effects in the treatment of rheumatoid arthritis, cortisone has been used in an ever increasing number of diseases and tuberculosis has been no exception. In American literature there are a few reports of small trials of both cortisone and A.C.T.H., either alone or in combination with streptomycin and para-amino salicylic acid (P.A.S.) in the treatment of advanced pulmonary tuberculosis. (Le Maistre *et al.*, 1951 ; Tompsett *et al.*, 1950 ; U.S. Veterans Administration Quarterly Progress Report, 1950). The results have not been encouraging. There was temporary and often marked symptomatic improvement but little evidence that the course of the disease had been altered. On the other hand Houghton (1952) reported marked clinical and radiological improvement in 6 of 8 patients with deteriorating or extensive pulmonary tuberculosis given courses of streptomycin P.A.S. and A.C.T.H. The improvement was maintained on withdrawal of A.C.T.H.

The possible danger of administering cortisone to the tuberculous subject has recently been stressed in medical literature both here and in America. There is clinical and experimental evidence that the hormone intensifies the tuberculous process. There have been numerous reports of activation of unsuspected tuberculosis in patients receiving cortisone or A.C.T.H. for rheumatoid arthritis or other diseases (Popp *et al.*, 1951 ; Doerner *et al.*, 1951 ; King *et al.*, 1951 ; Fred *et al.*, 1951). In the experimental animal most workers have found that both cortisone and A.C.T.H. cause a marked exacerbation of tuberculous infection (Michael *et al.*, 1950 ; Hart and Rees, 1950). There is evidence that Streptomycin does not prevent the deleterious action of cortisone or A.C.T.H. on experimental tuberculosis (Coste *et al.*, 1951 ; Karlson *et al.*, 1951).

The rationale for combined treatment is that cortisone with its lysing and inhibiting effect on granulation tissue might bring the tubercle bacilli " into the open " where they would come under the direct effect of the anti-tuberculous drugs. In this manner resolution of relatively chronic or indolent lesions might be accomplished. Bordley (1950) has demonstrated that both A.C.T.H. and cortisone

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reduce congestion, œdema and mucus production of chronically inflamed upper respiratory tract mucosa. Such an effect on the bronchial mucosa in tuberculous endobronchial disease might result in reaeration of atelectatic areas and perhaps reduction of resistant tension-type cavitation.

Methods

In view of the possible danger of cortisone in tuberculosis it seemed essential to tread warily in our investigations and, in particular, to direct our observations towards the early detection of deterioration from a local or generalised spread of the disease. To date 9 patients have been given cortisone combined with standard chemotherapy (streptomycin with P.A.S. and/or isoniazid (I.N.A.H.)) over a two-month period. Four had advanced bilateral disease with cavitation for which various courses of chemotherapy had been given in the past. The results of bacterial drug-resistance tests determined whether streptomycin was covered by P.A.S. and/or I.N.A.H. during cortisone treatment. In another 4 patients cortisone was added after a period of two to three months of the initial course of chemotherapy and where there was radiological evidence that the disease had become static. In one patient cortisone was given at the start of the first course of chemotherapy. In all patients chemotherapy was continued for at least two months after stopping cortisone. The dosage of cortisone was kept relatively constant for each patient and, initially, for safety, very small doses were used. The first patient received 12·5 m.g., the second and third 25 mg. and the remainder 50-100 mg. daily. The routine observations made were twice daily rectal temperatures and pulse rates, daily sputum measurements and a weekly clinical examination which included weight and B.S.R. The sputa were examined weekly by direct smear and, if necessary, culture. Chest X-rays were taken at fortnightly intervals and, as a special investigation, serial Mantoux tests were done before and at intervals during cortisone treatment.

Clinical Findings

General Symptomatic Effects; *Weight and B.S.R.*—The patients receiving 50-100 mg. of cortisone daily experienced a feeling of well-being with increase of appetite and strength and a lessening of cough. Even the smaller doses of cortisone (12·5 to 25 mg. daily) seemed to stimulate the appetite. The improvement in the general condition persisted even after cortisone was withdrawn. During combined treatment there was an early and progressive increase in weight (Table I). In 7 of 8 patients (one patient who died after six weeks cortisone is excluded from Tabes I and II) the weight gain after two months cortisone exceeded the weight gain during the previous two months; during this latter period the weight was either stationary or falling in 5 patients. Reference to the final column of Table I shows that the weight gain during cortisone was either increased,

maintained or had only relatively slightly fallen at the end of two months after stopping the drug.

In 7 of the 8 patients there was a fall in B.S.R. (Westergren) after two months' cortisone treatment (Table II). Usually the fall was prompt and in 2 patients on the higher dosage schedule B.S.R.'s of

TABLE I

Effect of Cortisone on Weight

Patient.	Cortisone Daily Mg.	Weight Change in 2 Months before Cortisone lbs.	Weight Change in 2 months of Cortisone lbs.	Weight Change in 2 Months after Cortisone lbs.
1.	12·5	+6	+12	−4
2.	25	−1	+10	+4
3.	25	−5	+ 5	+4
4.	50	+9	+13	+1
5.	50	0	0	0
7.	50-100	+6	+10	−1
8.	50-100	−3	+ 5	−2
9.	50-100	0	+ 7	−2
Average .	...	+1·5	+7·8	0

between 30 and 40 mm. per hour fell to single figures with one week of combined therapy. In most patients the B.S.R. quickly returned to its previous level when cortisone was withdrawn.

TABLE II

Effect of Cortisone on B.S.R.

Patient.	Cortisone Daily. Mg.	B.S.R. before Cortisone Mm./Hr.	B.S.R. after 2 Months Cortisone Mm./Hr.	B.S.R. 2 months after Cortisone Mm./Hr.
1.	12·5	37	24	20
2.	25	29	13	23
3.	25	28	9	8
4.	50	18	12	7
5.	50	19	11	15
7.	50-100	21	11	19
8.	50-100	34	14	42
9.	50-100	10	10	14

Details of Individual Cases

Case 1.—This patient, a 44 year old male, was admitted with a four weeks' history of fatigue, cough, dyspnœa and pain in the chest. X-ray of the chest showed widespread miliary opacities throughout the upper and mid zones of both lungs, the bases being clear. The sputum was positive for tubercle bacilli on direct examination. The diagnosis was considered to be hæmatogenous tuberculosis in a subacute phase. Chemotherapy was started with streptomycin 1 g. on alternate days, P.A.S. 20 g. daily and I.N.A.H. 200 mg. daily. After three months' treatment (streptomycin total 55 g.) chest X-rays showed that considerable resolution had occurred but this was by no means complete.

Reticular opacity persisted throughout the upper and mid zones of both lungs and suggested a fine residual fibrosis. Cortisone was added to the standard chemotherapy in doses of 12·5 mg. daily. After two months of this regime X-ray of chest showed that marked further resolution had occurred. There was now only residual streaky opacity at the right apex and a very fine reticular pattern in left upper zone. Two months after stopping cortisone the improvement had been maintained.

The amount of additional resolution which occurred after two months' cortisone treatment was surprising. It is a matter of opinion as to whether this would have occurred, and as quickly, on ordinary chemotherapy. Certainly this small dose of cortisone had no deleterious influence. It is possible that cortisone has prevented a permanent residual fine fibrosis.

The sputum, negative direct and on culture before cortisone, remained so throughout the two months' course.

CASE 2.—This patient, a 44 year old male had been under treatment in the sanatorium for a year with advanced bilateral fibro-caseous phthisis with widespread cavity formation. Despite intensive chemotherapy, which included streptomycin 95 g., P.A.S. and I.N.A.H., there had been no appreciable radiological change and the sputum had remained markedly positive on direct examination. Cortisone 25 mg. daily was given for a two-month period combined with streptomycin 1 g. on alternate days and I.N.A.H. 200 mg. daily. This treatment caused no significant radiological change. The sputum remained markedly positive throughout the two months' course.

The patient's general condition, however, improved and his weight, which had been static during the preceding two months, increased by 10 lbs. This gain in weight was maintained two months after stopping cortisone.

CASE 3.—This patient, a 62 year old male, was first seen in July 1950 when an X-ray of chest showed an old fibrotic lesion with excavation at the apex of the right lung. The sputum was positive direct. He refused admission and was followed-up as an out-patient. The right apical cavity gradually increased in size and the sputum remained positive. No chemotherapy was given. He eventually agreed to be admitted to the sanatorium in May 1953. X-ray of the chest showed a large chronic excavated area about 2 inches in diameter in the right upper lobe. Chemotherapy was started with streptomycin 1 g. on alternate days, P.A.S. 20 g. daily and cortisone 25 mg. daily. After two months of this combined treatment a P-A film of chest indicated that the cavity had closed. This was confirmed by a bucky film. Two months after withdrawing cortisone (the standard chemotherapy being continued) the cavity had remained closed and a series of tomograms failed to show any residual excavation. The sputum was positive direct throughout the two months' course of cortisone but two weeks after stopping cortisone it became negative both direct and on culture and remained so.

Again it is a matter of opinion but it is unlikely that such a large chronic cavity would have closed after two months' ordinary chemotherapy.

CASE 4.—This patient, a 27 year old female, was first admitted to the sanatorium in 1951 with extensive bilateral tuberculosis with excavation. After one month she discharged herself irregularly. She refused repeated requests to be readmitted but eventually agreed in April 1953. An X-ray of

chest on admission showed extensive active bilateral pulmonary tuberculosis. There was dense mottling throughout with cavitation in both upper zones. The sputum was positive direct. Chemotherapy was started with streptomycin 1 g. daily for three weeks then 1 g. on alternate days, P.A.S. 18 g. daily and I.N.A.H. 200 mg. daily. Initially there was considerable improvement but after $3\frac{1}{2}$ months' chemotherapy (streptomycin total 64 g.) the disease was considered radiologically to be static or slightly deteriorating. There was still widespread opacity in both lungs with obvious cavitation in the right upper and mid zones. Cortisone was added to the chemotherapy in doses of 50 mg. daily. After two months of this combined therapy an X-ray of chest showed that considerable further resolution had occurred especially in the left lung. The right upper zone cavity had shrunk to about half its size and the right mid zone cavity was no longer obvious. Two months after stopping cortisone the improvement had been maintained. Soon after admission the patient surprisingly became unable to produce a specimen of sputum. Recourse was made to gastric lavage and this was positive on direct examination before and at the end of two months' cortisone course.

In this case cortisone appears to have had a definite beneficial effect when the disease appeared to be static or deteriorating. The patient's general condition greatly improved during combined treatment. Her weight increased by 13 lbs. in the two months and this increase was maintained two months after stopping cortisone. She had her first menstrual period for ten months during cortisone administration.

CASE 5.—This patient, a 33 year old male, was admitted in March 1952 when an X-ray of chest showed extensive active bilateral tuberculosis with cavitation affecting the upper and mid zones of both lungs. He was treated with prolonged and intensive chemotherapy which included 102 g. of streptomycin, P.A.S. and I.N.A.H. Despite this, the disease was never controlled and the sputum remained markedly positive. Bacterial drug resistance tests eventually showed a high degree of resistance to streptomycin and complete resistance to I.N.A.H. In view of the very poor prognosis, cortisone 50 mg. daily combined with streptomycin 1 g. on alternate days and P.A.S. 20 g. daily was given for two months. This treatment produced no appreciable clinical or radiological change. The sputum remained positive direct throughout.

Despite the poor chemotherapeutic cover, there was no evidence of deterioration as a result of a two months' course of cortisone in doses of 50 mg. daily.

CASE 6.—This patient, a 33 year old male, was first seen in November 1948 with lung lesions strongly suggesting sarcoidosis. He failed to attend for follow-up examination and was not seen again until February 1952. He was then in an extremely toxic condition and re-X-ray of chest showed gross tuberculous infiltration with multiple areas of excavation throughout almost the whole of both lungs. He was admitted to the sanatorium but failed to respond to prolonged and intensive chemotherapy. Eventually bacterial drug-resistance tests showed moderate resistance to streptomycin and I.N.A.H. Despite this, and especially as he appeared to be entering the terminal phase of his illness, it was decided to give cortisone 100 mg. daily combined with streptomycin 1 g. on alternate days and I.N.A.H. 200 mg. daily. The initial symptomatic improvement was quite remarkable. The temperature, which had been running between 100 and 103° F. for many months fell to normal in two days. The appetite greatly improved, dyspnœa lessened and his strength

increased. A weight increase of 11½ lbs. in the first week was obviously partly due to fluid retention. Unfortunately this improvement was not maintained. Cortisone appeared to be overloading the circulation and the dosage was reduced to 50 mg. daily. Pyrexia reappeared and his general condition progressively deteriorated. There was a sudden onset of severe diarrhœa with the passage of blood and mucus, which could not be controlled and continued until death, six weeks after starting cortisone.

I am indebted to Dr A. L. Scott of Dumfries and Galloway Royal Infirmary for the *post-mortem examination*. This showed advanced bilateral phthisis. Both lungs were extremely friable and sections produced a sensation of cutting soft cheese. There was little evidence of fibrosis but extensive caseation and cavitation. There were no tuberculous lesions elsewhere in the body.

On *histological examination* of the lungs the striking feature was the degree of vascularity associated with the caseous lesions. The walls around the cavities showed little fibrosis and both epitheloid cells and lymphocytes were scanty. The caseous material was loose and vacuolated in places and near the periphery appeared to be undergoing resorption.

This histological appearance bears a remarkable resemblance to that described by Dick (1953) in renal tuberculosis treated with I.N.A.H. alone. The initial chemotherapy in the present case was a three months' course of I.N.A.H. and later the patient had a total of eight months I.N.A.H. combined with streptomycin and P.A.S. The final course of chemotherapy included I.N.A.H. It is impossible to say what part cortisone has played in the histological picture described. The appearance may quite well have been due to I.N.A.H.

Before starting cortisone the patient was considered to be in the terminal phase of his illness and it is difficult to be certain whether or not the drug hastened his death.

Case 7.—This patient, a 46 year old female, was admitted in July 1953 with a two months' history of malaise, cough and sputum. An X-ray of chest showed dense opacity of almost the whole of the upper lobe of the right lung with a possible area of central softening. The lesion suggested partial atelectasis in addition to infiltration and caseation. The sputum was positive direct. Treatment with streptomycin 1 g. on alternate days, P.A.S. 18 g. daily and I.N.A.H. 200 mg. daily was started. After one month's chemotherapy definite resolution had occurred but X-rays at two and three months showed little change and the disease was judged to be static. Cortisone was added to the chemotherapy in doses which varied between 50 and 100 mg. daily (average daily dose was approximately 75 mg.) for two months. This resulted in obvious further resolution amounting to about 50 per cent. when compared with the previous area of static disease. In the two months following the withdrawal of cortisone there was no significant change in the radiological appearances. The sputum, negative direct and on culture before cortisone, remained so both during the two months' course and the subsequent two months.

In this case after three months' chemotherapy the disease was radiologically static and the further considerable resolution which occurred would appear to be due to cortisone.

Case 8.—This patient, a 28 year old female, was admitted in January 1950 in an extremely toxic condition, with bilateral upper zone disease with excavation. The sputum was positive direct. From January 1950 until February

1953 she had frequent courses of chemotherapy which included streptomycin 99 g., P.A.S., I.N.A.H. and the thiosemicarbazones T.B. 1 and 3. Despite this the sputum remained positive direct and bilateral excavation persisted. In November 1953 treatment with cortisone was begun in doses of 100 mg. daily for one week, then 50 mg. daily for two weeks, followed by 75 mg. daily for the remainder of the two months' period. This was combined with streptomycin 1 g. bi-weekly and P.A.S. 18 g. daily. Prior to this treatment X-ray of chest showed a tension type cavity in each upper lobe which had persisted relatively unchanged for many months. On the right side the cavity measured 1 cm. in diameter while on the left side the diameter was 3 inches. After two months of combined treatment the right upper zone cavity was no longer obvious and the cavity in the left upper zone was only slightly smaller. Tomograms of the right upper zone showed in fact that residual excavation was still present on this side. Prior to cortisone the sputum was positive direct. At the end of the two months' course it was negative direct but positive on culture.

The improvement in this patient was disappointing as it was hoped that cortisone might have relieved bronchiolar obstruction. On the other hand tension cavitation was known to have been present for over three years.

CASE 9.—This patient, a 53 year old male, was first seen in October 1952 when an X-ray of chest showed restricted right upper zone mottling and a more obvious left mid zone infiltration. The lesions were judged to be of low activity. Out-patient follow-up showed little radiological change but one scanty positive direct smear was obtained in December 1952. He was admitted to the sanatorium in August 1953 as there seemed to be slight extension of the left mid zone infiltration. There was no radiological improvement after a three months' course of streptomycin 1 g. on alternate days with I.N.A H. 200 mg. daily, and cortisone, 100 mg. daily for six weeks followed by 50 mg. daily for two weeks, was added to the chemotherapy. This combined therapy was without significant effect. The sputum negative direct and on culture since admission remained so throughout the two months' course of cortisone and also during the subsequent two months.

In retrospect the clinical and radiological features of this case suggested that bronchiectasis might be the dominant pathological feature of the left mid zone infiltration. A bronchogram, however, showed a normal bronchial tree. Again, it was disappointing that combined treatment had failed to resolve an apparently indolent tuberculous lesion.

TOXIC EFFECTS OF CORTISONE

Excluding the one fatality of which the relationship to cortisone is uncertain, no serious toxic effects were noted in the remaining 8 patients. Those who received the higher doses of 50 to 100 mg. daily showed some rounding of the facial contours and one of these patients had a definite "moon-face." There was no instance of clinical exacerbation of the disease either local or general by hæmatogenous dissemination. No frank hæmoptysis occurred. One patient showed slight staining of the sputum during cortisone but this had been a periodic occurrence during the preceding months.

The Effect of Cortisone on the Bacteriology of the Sputum

Sputa were examined personally by direct smear at weekly intervals during cortisone treatment and for the following two months. Specimens were sent for culture at fortnightly intervals in those patients negative direct and on culture prior to cortisone. It was thought that frequent examination of direct smears would aid the early detection of a possible recrudescence of the disease; this applied especially to the patients with negative sputa before cortisone and who received the higher dosage schedule.

The results are summarised in Table III. The sputa are simply

TABLE III

Effect of Cortisone on the Bacteriology of the Sputum

Patient.	Cortisone Daily Mgm.	Sputum before Cortisone Dir.	Sputum before Cortisone Cult.	Sputum During Cortisone. Week 1 Dir.	Week 1 Cult.	Week 2 Dir.	Week 2 Cult.	Week 3 Dir.	Week 3 Cult.	Week 4 Dir.	Week 4 Cult.	Week 5 Dir.	Week 5 Cult.	Week 6 Dir.	Week 6 Cult.	Week 7 Dir.	Week 7 Cult.	Week 8 Dir.	Week 8 Cult.
1.	12·5	−	−							−	−							−	−
2.	25	+		+		+		+		+		+		+		+		+	
3.	25	+		+		+		+		+		+		+		+		+	
4.	50	+	−															+	−
		G.L.																G.L.	
5.	50	+		+		+		+		+		+		+		+		+	
6.	50-100	+		+		+		+		+		+		+					
7.	50-100	−	−	−		−	−	−		−	−	−		−	−	−		−	−
8.	50-100	+		+		−	+	+		−	+	+				+		−	+
9.	50-100	−	−	−		−	−	−		−	−	−		−	−	−		−	−

recorded as positive or negative, direct or on culture and no attempt is made to assess quantitatively the degree of positivity. Patient 4 had no sputum and gastric lavage was done before and at the end of two months' cortisone. The main feature is that in the 9 patients no significant change has occurred in the bacteriology of the sputum throughout cortisone treatment. Four patients (2, 3, 5 and 6) had positive direct smears before starting cortisone and the sputa remained positive throughout. (No persistent alteration in the degree of positivity was noted.) Three patients (1, 7 and 9) who were negative direct and on culture remained so throughout cortisone. Two of these 3 patients (7 and 9) were receiving 50-100 mg. cortisone daily. Patient 4 had a direct positive gastric lavage at the beginning and end of cortisone treatment. Patient 8 positive direct prior to cortisone produced an occasional negative smear, positive on culture during treatment.

In 6 of the 8 patients observed during the two months following withdrawal of cortisone the sputum results showed no change from those recorded in Table III. Patient 2 became sputum negative direct and on culture two weeks after withdrawal of cortisone and remained so. Patient 4 had negative gastric lavages direct and on culture at one and two months after cortisone treatment.

Cortisone and Tuberculin Sensitivity

Mantoux tests, using three dilutions of old tuberculin (1/1000, 1/10,000, 1/100,000) were performed on each patient before and at intervals of one to four weeks during cortisone. The same stock solution of old tuberculin was used throughout and the dilutions were freshly made for each test series. The results are summarised in Table IV.

A small o signifies no change, an ↑ increased reaction and an ↓ diminished reaction. A, B and C represent dilutions of 1/1000, 1/10,000 and 1/100,000 respectively. The results are related to the pre-cortisone series. Both the diameter and the thickness of the lesions were measured. A significant change in tuberculin sensitivity is recorded

TABLE IV

Effect of Cortisone on Skin Sensitivity to Tuberculin

Patient.	Cortisone Daily. Mgm.	Tuberculin Sensitivity During Cortisone.															
		Week 1			Week 2			Week 3			Week 4			Week 5			Week 6			Week 7			Week 8		
		A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1.	12·5				o	o	o				↓	o	o				o	o	o				o	o	o
2.	25				↑	↑	o				↑	o	↓										o	o	↓
3.	25				↑	o	↑				↓	↓	o										o	o	o
4.	50				o	o	o													o	o	o			
5.	50				o	o	o	o	o	o							o	o	o				o	o	o
6.	50-100				↑	o	o																		
7.	50-100				o	o	o				o	o	o				↓	↓	o				↓	o	o
8.	50-100	↓	o	o				↓	↓	o										↓	↓	o			
9.	50-100				↑	o	o				↓	↓	o										↓	↓	o

only if there is a diameter change of 8 mm. or more or a thickness change of at least 4 mm. Four of the patients were originally insensitive to the 1/100,000 dilution. In no case did complete insensitivity to either of the three dilutions occur at any of the tests during cortisone administration. There was definite reduction in sensitivity at some point during cortisone in three patients receiving 50-100 mg. daily (patients 7, 8 and 9). Two patients (6 and 9) on 50-100 mg. daily and 2 (2 and 3) on 25 mg. daily showed increased reaction to one or two of the dilutions when tested at the end of the second week of cortisone. Two patients (4 and 5), on 50 mg. daily showed no significant change throughout. Overall, no dramatic change was noted. The impression gained is that the larger doses of cortisone cause a slight diminution in tuberculin sensitivity.

Discussion

There has been remarkable progress in the treatment of tuberculosis during the past five years. The introduction of streptomycin, P.A.S. and more recently I.N.A.H. has vastly improved the prognosis in the great majority of cases of pulmonary tuberculosis. However, the limitations of modern chemotherapy are now being more clearly defined. The emergence of drug resistant bacilli has been well substantiated but already much knowledge has accumulated on the

prevention or delay of resistance by using combinations of the anti-tuberculous drugs in adequate dosage. Nevertheless, there remain a substantial number of patients in whom the disease does not or only partially responds to chemotherapy and where the bacilli are sensitive to the drugs being used. This may result from a combination of factors concerned with host resistance but it seems reasonable that in some of these cases the drugs are unable to penetrate fibrous or granulation tissue barriers. It is for this reason that cortisone combined with standard chemotherapy might have a beneficial influence on certain forms of pulmonary tuberculosis. It is quite obvious that the preliminary and uncontrolled observations reported in this paper can only be interpreted very superficially.

There is no doubt that definite symptomatic improvement resulted from cortisone treatment; a feeling of well-being, improvement in the general condition with increase in appetite and weight have all been common features. In many of the diseases in which cortisone is effective, *e.g.* rheumatoid arthritis, it is well known that recrudescence occurs on stopping the drug; this has been called the "rebound phenomenon." In the present investigation no obvious clinical deterioration occurred on cortisone withdrawal apart from a reduction of appetite which was previously excessive and a return of the B.S.R. to its pre-cortisone level. It is of interest that the gain in weight observed in 7 of 8 patients studied was largely maintained during the two months after cortisone was stopped. It may be that in tuberculosis where cortisone is being used to facilitate the effect of the anti-tuberculous drugs the improvement obtained either symptomatic or organic might be permanent.

The important, and in view of the results of animal experiments, the surprising observation is that cortisone with chemotherapeutic cover has not caused an acute exacerbation of tuberculosis, either local or generalised. It must be emphasised that in the experimental animal the doses of cortisone used have been relatively huge and it may well be that equivalent dosage in the human being would produce disastrous effects. In the present investigation the chemotherapy was known to be partially ineffective in at least 2 of the patients, yet no obvious deterioration resulted from cortisone. The anti-tuberculous drugs seem able to deal effectively with any bacilli which may be allowed to emerge or proliferate under the influence of cortisone. In 4 of the 9 patients the radiological improvement during cortisone appeared to be greater or quicker than could be expected from chemotherapy alone. Hæmatogenous tuberculosis in a subacute phase underwent relatively rapid and complete resolution. A large chronic upper zone cavity, known to have been present for at least three years, closed within two months. In 2 patients on higher dosage the disease was considered to be static despite full chemotherapy and further definite improvement occurred on introducing cortisone.

The observed slight diminution in tuberculin sensitivity on the higher dosage of cortisone coincides with published reports. Skin

sensitivity has been reported to be depressed by cortisone in animals (Long and Miles, 1950) and in man (Le Maistre *et al.*, 1951); some workers have found little or no change (Bogen *et al.*, 1951) or even an increased reaction (Coste *et al.*, 1951).

The conclusion we would draw is that the possibility of cortisone having a beneficial influence in tuberculosis should be further explored using the small as well as the larger dosage. If further experience confirms that this treatment is safe, then the field of therapeutic trial becomes greatly increased. It may be possible to achieve complete resolution and sterilisation of relatively early infiltrative lesions and so prevent the likelihood of recurrence of disease. The indolent tuberculous lesions for which in the past tuberculin treatment has been tried may with benefit be stirred up by cortisone. Also it might be worthwhile trying the effect of combined therapy in primary tuberculosis in children, where bronchial pressure is causing persistent atelectasis.

Cortisone is a potentially dangerous substance in any infection and especially in tuberculosis where hæmatogenous dissemination might be disastrous. It must be emphasised that the use of this drug in tuberculosis is at present purely experimental and requires the most strict clinical, bacteriological and radiological control. Whether cortisone may prove to have any place in the treatment of tuberculosis can only be ascertained by further careful trial.

Summary

This paper is a preliminary report of the treatment of pulmonary tuberculosis by cortisone combined with standard chemotherapy. The clinical, radiological and bacteriological findings are presented in 9 patients. Definite symptomatic improvement was commonly observed and, in particular, gain in weight would appear to be permanent. In 4 patients the radiological improvement was greater than could have been expected from ordinary chemotherapy. Apart from one fatality, of which the relationship to cortisone is uncertain, there was no evidence of exacerbation of tuberculosis during or following cortisone administration. It is considered that the results are sufficiently encouraging to warrant an extended trial.

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REFERENCES

Bogen, E., Netzer, S., and Salkin, D. (1951), *Trans. 10th Conf. Chemotherapy of Tuberc.*, p. 251.

Bordley, J. E. (1950), *Bull. Johns Hopkins Hosp.*, **87**, 482.

Coste, F., and Blatrix, C. L. (1951), *Rev. Tuberc.*, Paris, **15**, 698.

Dick, J. C. (1953), *Lancet*, **1**, 808.

Doerner, A. A., Naegele, C. F., Regan, F. D., and Cameron, G. F. (1951), *Amer. Rev. Tuberc.*, **64**, 564.

FRED, L., LEVIN, M. H., RIVO, J. B., and BARRETT, T. F. (1951), *Journ. Amer. Med. Assoc.*, **147**, 242.

HART, P. D'A., and REES, R. J. (1950), *Lancet*, **2**, 391.

HENCH, P. S., KENDALL, E. C., SLOCUMB, C. H., and POLLEY, H. F. (1949), *Proc. Mayo Clin.*, **24**, 181.

HOUGHTON, L. (1952), *Tubercle*, **33**, 381.

KARLSON, A. G., and GAINER, J. H. (1951), *Dis. Chest.*, **20**, 469.

KING, E. Q., JOHNSON, J. B., BATTEN, G. S., and HENRY, W. L. (1951), *Journ. Amer. Med. Assoc.*, **147**, 238.

LE MAISTRE, C. A., TOMPSETT, R., MUSCHENHEIM, C., MOORE, J. A., and MCDERMOTT, W. (1951), *Journ. Clin. Invest.*, **30**, 445.

LONG, D. A., and MILES, A. A. (1950), *Lancet*, **1**, 492.

MICHAEL, M., CUMMINGS, M. M., and BLOOM, W. L. (1950), *Proc. Soc. Esp. Biol. N.Y.*, **75**, 613.

POPP, C. G., OTTOSEN, P., and BRASHER, C. A. (1951), *Journ. Amer. Med. Assoc.*, **147**, 241.

TOMPSETT, H., LE MAISTRE, C. A., MUSCHENHEIM, C., and MCDERMOTT, W. (1950), *Journ. Clin. Invest.*, **29**, 849.

U.S. Veterans Admin. Quart. Progress Report, October 1950, p. 23.