STREPTOMYCIN FOR CHRONIC AMBULANT TUBERCULOUS PATIENTS

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The use of streptomycin for the treatment of pulmonary tuberculosis has been so intensively studied that it is surprising how little consideration has been given to the largest group of all tuberculous patients—those whose disease is chronic but not incapacitating—who have survived the acute stage of the disease and its accompaniment of treatment, but who will still carry a permanent disability. The early trials, it is true, concerned those whose disease was so advanced that no active treatment was possible, thereby giving moral justification to experiment: later work has been almost exclusively concerned with the clear indications for chemotherapy, such as acute and early exudative disease, tracheo-bronchial disease, and in association with thoracic surgery.

The chronic case has been almost ignored, either because the results are not dramatic enough to arrest attention or because the real nature of the problem has not been properly appreciated. With almost casual indifference most writers and lecturers dismiss the chronic type of disease as beyond the aid of streptomycin. This attitude is probably due to the exaggerated importance given to the x-ray appearances, and the fact that so many chronic cases do have extensive cavitation, the course of which is used as the measure of improvement. Streptomycin, of course, cannot of itself close cavities, except in certain cases by its effect upon active bronchial disease. In the type of patient who is now under consideration, however, the radiological appearances are, in any case, unlikely to change very much even as the years pass by, and some other criteria should be used to assess the value of treatment: here, indeed, more than in any other group, is it true that treatment must be directed at the patient and not at his x-ray film.

Streptomycin differs from other therapeutic measures in its direct attack on the tubercle bacillus, and in certain types of chronic tuberculosis a bacteriological standard is much more valuable than a radiological one: sputum conversion should be a major aim of treatment. This fact is clearly stated by Tucker (1949): "There can be little quarrel with the validity of sputum conversion as an index of therapy of which streptomycin may be a part."

An investigation has therefore been done to determine the value of streptomycin for this purpose in patients whose only clinical sign of activity has been the persistently positive sputum. The cases have been deliberately selected because they seemed likely to benefit by the treatment, and Fig. 1, which depicts the results of the trial, also indicates the various periods of observation which have been possible. All patients had been under observation for at least six months, and many for more than two years, before starting streptomycin.

The results have been so successful that they have opened up a large field of valuable therapy, and if the continued follow-up confirms the early impressions a most important step will have been taken in the control of tuberculosis.

FIG. 1.—Sputum state before and after streptomycin.

Selection of Cases

The investigation was started in February, 1950, and the patients chosen were those whose sputum was persistently positive on fluorescent microscopy or culture but who showed no other signs of clinical activity. They were all men or women working in the Papworth Industries under medical supervision, and living a comparatively normal life. Radiologically there had been little if any change for many months or years; they were regularly afebrile, the blood sedimentation rates were normal, their weight was steady, and the quantity of sputum varied from a trace in the early morning to 2 oz. (57 ml.) daily. No change was made in their normal routine during this treatment.

The following types were included: (1) Patients with widespread chronic fibrotic disease without evidence of gross cavitation, and certainly unsuitable for surgery. (2) Patients in whom a pneumothorax had been established for some months, and in whom the sputum, previously negative, had suddenly become consistently positive. In these cases tomography was done to exclude persistent cavitation. (3) Patients in whom thoracoplasty had failed to convert the sputum, or in whom the sputum had subsequently reverted to positive. (4) Patients in whom the disease had apparently healed by fibrosis and contraction, leaving a slight bronchiectatic condition, but who were unsuitable, or unwilling, for major surgery: it is usually the upper lobes which are thus affected. (5) One patient (Case 18) has been included as an interesting contrast though he did not really fit into this category. He had bilateral apical disease, with fibrosis and contraction, but tomography showed cavitation, 1 in. (2.5 cm.) in diameter, on one side. He refused surgery, and as his general condition was otherwise excellent he was given a course of ambulant chemotherapy, but the sputum was not converted. (Fortunately his views have now been converted instead.)

Sputum Tests

The following standards were observed:

1. Three consecutive positive sputa were obtained before beginning chemotherapy. In those patients in whom a positive sputum was noted for the first time, or there was

a reversion after a period of negative sputa, three more samples taken during a period of about one month were tested to confirm the finding.

2. In most cases samples were tested at monthly intervals during chemotherapy, fortnightly for two months afterwards, and subsequently monthly up to the time of writing.

3. Only 24-hour samples were used; if sputum was not available three laryngeal swabs were used instead of one 24-hour specimen.

4. Sputum was examined by fluorescent microscopy (Cruickshank, 1947) and culture on Löwenstein's medium: a negative report refers to six weeks' culture.

5. The sputum of every patient was tested for streptomycin sensitivity before treatment and found sensitive to 1 unit of streptomycin per ml.

Plan of Treatment

Before starting treatment tomography was done, when necessary, to exclude gross cavitation: in many cases bronchoscopy was also performed and the reports were uniformly normal, thereby excluding tuberculous disease of the larger bronchi as the cause of the positive sputum, since this would demand more drastic treatment. The bronchial aspirate, however, gave further confirmation of the presence of tubercle bacilli.

The course of treatment at first was 1 g. of streptomycin daily intramuscularly, usually for 90 days. P.A.S., 14.1 g. daily; in tablet and cachet form, was given concurrently according to the technique described by Battersby *et al.* (1950). The streptomycin dose has now been reduced to 1 g. twice weekly, for 26 doses, as suggested by recent reports (Veterans Administration, 1951).

Results

The clinical details of these patients are shown in Fig. 1, in which the contrast in the sputum status before and after streptomycin is depicted graphically. The patients are considered in four groups.

A. Chronic Bilateral Disease.—Seven men, aged 19–42, had chronic bilateral fibrotic disease which was too extensive for major surgery. Earlier treatment had included medical collapse measures, but in every case the sputum had remained consistently tubercle-positive whilst the patients were under observation at Papworth, which was 6–24 months. There was no gross cavitation. Three of the patients have remained sputum negative. Case 1, the first of the series, was given only 42 g. of streptomycin, and the sputum remained converted for a year. He was then positive to three successive tests, and a further short course of streptomycin was given, which has effectively controlled the disease so far. It is of interest that the two patients given 1 g. twice weekly remained tuberculosis-negative for only about six months, but the chemotherapy will be repeated.

B. Pneumothorax or Pneumoperitoneum.—Six cases had an established collapse measure, but the sputum was consistently or intermittently positive: in Cases 8, 10, 11, and 13 there was also slight disease in the opposite lung. All except one of these patients converted the sputum permanently, and remained tuberculosis-negative up to the time of writing. One man who had been tuberculosis-positive for the previous two years did produce intermittent positive sputum after seven months, but has again been negative for six months.

C. After Thoracoplasty.—Four cases were chosen in whom thoracoplasty had been done and in whom the sputum had subsequently been positive for at least a year. All have remained negative since chemotherapy.

D. Localized Fibrotic Lesion.—Seven cases had localized unilateral or bilateral fibrotic disease; of these, one (Case 18) also had definite cavitation, and was included because he refused surgery (see above). Of the other six, three have produced one positive sputum since chemotherapy but subsequent tests have been negative, and one has been consistently negative despite being positive for two years pre-

viously. Case 22 was given only 1 g. twice weekly, and, although converted at first, he produced positive sputum after five months: unfortunately he left Papworth and has been lost sight of.

Summary of Results

Group:	A	B	C	D	Total
No. in group	7	6	4	7	24
Initial conversion	7	6	4	6	23
Follow-up:					
All tests negative	3	5	4	2	14
Isolated positive	1	1	0	3	5
Reverted	3	0	0	1	4

The Table shows that of 24 cases with a previously persistent positive sputum, 14 have been entirely sputum-negative since treatment. In five cases an isolated specimen has been positive but subsequent samples negative, and in four cases the sputum which had been converted has subsequently become again positive: three of these received intermittent streptomycin treatment, to a total of only 26 g.

Similar Group (Untreated) for Comparison

The problem of comparable controls in tuberculosis is always difficult and no attempt has been made at alternate selection for this purpose. However, it seemed desirable to compare these results with those of patients in other hostels or under another physician who were living under similar conditions and also working in the Papworth Industries. All such patients who seemed to fall into the same four groups, and who had persistently positive sputum during 1950, were therefore studied; the sputum state of these people is depicted in Fig. 2, the period of observation available being at least a year: no patients with artificial pneumothorax and positive sputum were available, as other forms of active treatment had been initiated.

FIG. 2.—Sputum state of untreated group.

On comparison of Figs. 1 and 2 it is immediately obvious that, although certain cases do revert spontaneously—as is well known—there is no clear-cut change such as is seen after streptomycin in Fig. 1.

In addition, of course, the sputum history of most of the patients in the trial series had been recorded during the previous six months to two years, as shown in the left-hand side of Fig. 1, and this record also affords comparison with the post-streptomycin condition.

Complications

Three types of complication might be expected: (1) toxic symptoms due to streptomycin or P.A.S.; (2) development of a resistant strain of tubercle bacillus; and (3) clinical deterioration.

1. *Toxic Symptoms*.—Since these men and women were continuing at work and living a normal active life during treatment, it was feared that such symptoms as giddiness, visual or aural disturbances, nausea, or diarrhoea would seriously incapacitate them or even be dangerous to those moving among traffic and heavy machinery. No such symptoms have developed in the 24 cases treated, and even the usual abdominal symptoms due to P.A.S. have been much less than is found in bed-patients. In only one case has the diarrhoea due to P.A.S. necessitated a short period off work, and this was ultimately controlled by kaolin. The patients themselves have volunteered the opinion that P.A.S. is much more easily tolerated when they are up and about than when in bed.

2. *Resistant Strains*.—In a community such as Papworth Village Settlement the development of resistant strains of *Mycobacterium tuberculosis* would of course become a serious threat to the families, and before the routine use of P.A.S. this danger would have been very real. In no case in this series has an organism developed resistance to 1 unit of streptomycin per ml. This is in accord with the general opinion to-day that the combination of streptomycin with P.A.S. reduces the incidence of resistant strains from about 70% to 8% (Dunner *et al.*, 1949), or may completely prevent such a complication (Tempel *et al.*, 1950; Hughes *et al.*, 1951). The development of resistance to P.A.S. (Carstensen and Andersen, 1950) need not be regarded as a serious problem when compared with the tremendous value of sputum conversion.

3. *Clinical Deterioration*.—The cases were selected carefully, and in no instance has there been clinical deterioration. It is agreed that if patients who really require rest, collapse therapy, or major surgery are treated by ambulant chemotherapy, then the clinician will be practising bad medicine and cannot expect good results. Similarly, extensive cavitation has often been shown to be unsuitable for streptomycin (Tempel and Dye, 1949; Riggins and Hinshaw, 1949), although in such patients chemotherapy may be helpful in preventing deterioration whilst awaiting surgery. The usual criteria of weight, well-being, E.S.R., temperature, and x-ray appearances were noted throughout the period of follow-up, and in general there was little change. This only indicates the type of disease studied, in which the positive sputum was the main adverse clinical finding.

Discussion

Topical interest is focused on the falling death rate for pulmonary tuberculosis, but this fact combined with intensified survey work may well aggravate the immediate public health problem. The chronic patient who is kept alive in 1952 must be controlled, and if possible employed, and even the most enthusiastic physician will hardly claim that all such patients can be really cured and rendered non-infectious. Heaf (1951) mentions a figure of 140,000 persons "at large in England and Wales . . . and potential sources of infection," and of these a large proportion will be of the type referred to by Gloyne (1946) as "indolent tuberculosis."

In America the expression "grumblers" is used (Howlett and O'Connor, 1948), a term which describes both the clinical condition and often, alas, the mental state which is engendered by the lack of treatment or employment and by the surfeit of commonplace advice.

If we feel it our duty to prolong life, it must also be our duty to do everything in our power to enable these persons to obtain such employment as is within their powers. Longevity without peace of mind or economic independence is a sad prospect.

The problem of the "good chronic" is the most tragic and difficult in tuberculosis work, and the patients chosen for this series represent those who do attend at every clinic and promote anxious discussion among chest physicians. Such patients are often able and willing to work, being in fact compelled by economic pressure to do so. Yet employers and physicians take fright at the thought of possible infection. At a recent interview, 10 out of 14 men wishing to come to Papworth had been prevented by their tuberculosis officer from obtaining local employment because the sputum was positive, and this enforced and unnecessary idleness had lasted from one to three and a half years. One should think not only of the personal tragedy involved but the economic cost of unemployment, and the frustration and incompleteness of medical care.

Neither medical nor surgical treatment is yet completely curative, and thoracoplasty often leaves a persistent positive sputum although the disease appears inactive (Holmes Sellors, 1947; Thompson, 1951; M.R.C., 1951). Gutheil *et al.* (1950) reported 20% of cases with a positive sputum 10 years after thoracoplasty, and successfully used streptomycin for sputum conversion. These are the men and women who should be helped back to employment and more certain cure.

The significance of a positive sputum will not be discussed fully, but reference can be made to Berg (1939), Chang (1948), Abeles (1948), and Brieger (personal communication), who have shown that the survival rate is considerably lower in patients with a positive sputum, and the incidence of relapse is higher. This applies even to the patient with intermittently positive sputum after apparently adequate treatment. The importance of the public health problem, of course, needs no emphasis, and the dictum of Tucker (see above) will be generally approved.

The results of this series have shown that in selected types of cases the social and medical disadvantage of an infectious sputum can be prevented without interfering with the usual routine of life. The patients continued their active work and social life during treatment, remaining economically independent and able to support their families without assistance.

The same possibility exists for physicians working from chest clinics, and there is no reason why such treatment should not be given either in the out-patient department or by visits from the clinic nursing staff: there would be no need for a man to give up his employment. If further study confirms the results of Tempel and Dye (1949) and of most speakers at the tenth Streptomycin Conference (Veterans Administration, 1951) that intermittent dosage is equally effective, the arrangements for treatment at a clinic would require only simple organization.

The cost of such treatment would be negligible compared with the cost of financing unnecessary idleness, even though different sections of the Exchequer were concerned.

Warning must be given, of course, that it is essential for such treatment to be under the direction of a chest physician with adequate facilities for bacteriological control.

Conclusion

The physician to-day should not be satisfied with merely rendering his patient quiescent and jogging him along "under careful observation," State-supported, and only half enjoying life. The goal should be a man whose disease is inactive, who is financially independent, and who is no risk

to his family or colleagues. With this in view, there is considerable scope for chemotherapy in certain types of more chronic patients whose only real disability is an infectious sputum, and this series of cases has shown that the sputum can be converted without interfering with the ordinary day's work.

Summary

Streptomycin and P.A.S. have been used for certain types of patient whose only adverse clinical sign was a positive sputum. Twenty-four patients, in four categories, whose sputum was consistently positive, were treated without interfering with their work or ordinary life.

In 23 cases the sputum was converted; in 14 of them it has remained negative up to two years. Five patients have since had an isolated positive sputum, and four have reverted to positive sputa after being sputum-negative for a period.

The value of such results is discussed when applied to the problem of employable chronic patients, so commonly attending chest clinics.

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The possibility of using high-velocity electrons and gamma rays for sterilizing pharmaceutical products was discussed by Government scientists and representatives of the pharmaceutical industry at a recent meeting at the Department for Scientific and Industrial Research. The method, according to Dr. R. S. Hannan, who has been studying the problem in America, has several advantages: it permits the sterilization of heat-sensitive materials; almost any type of sealed container can be used for the process; and it may lead to the preparation of new products, such as new vaccines. One of the disadvantages is the high capital cost of the generating equipment. Electron accelerators at present available in Britain, capable of treating 1 cwt. (51 kg.) of product an hour, cost between £25,000 and £50,000. A cobalt 60 source for producing gamma rays in sufficient quantity to sterilize 7 lb. (3 kg.) a day would cost £2,000, but gamma rays from fission products would be much cheaper. Other disadvantages, perhaps more theoretical than practical, are toxicity from unusual chemical by-products of irradiation and the failure to inactivate enzymes. The energies used for sterilization are insufficient to induce radioactivity in treated products. So far most of the work in this country on "electronic sterilization" has been done in relation to food; however, its uses in this field may be limited because of alterations to flavour.

ACQUIRED HYPERSENSITIVITY TO SODIUM P.A.S., STREPTOMYCIN, AND PENICILLIN

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The administration of sodium *p*-aminosalicylate together with streptomycin is at present the most effective form of chemotherapy for tuberculosis. Toxic effects, while not infrequent, are usually of minor degree. Occasionally streptomycin produces a more severe reaction, such as exfoliative dermatitis or agranulocytosis, which may endanger life. The liver, however, generally appears to escape damage and jaundice is not a feature.

It was at first thought that the toxic effects of P.A.S. were mostly confined to the alimentary tract, the characteristic symptoms being nausea, vomiting, and looseness of the bowels; these disappeared rapidly on stopping the drug. Recently, however, it has become apparent that a small proportion of patients can develop an acute hypersensitivity with severe systemic upset, and a number of reports (Cuthbert, 1950; Livingstone and Street, 1950; Hess and Ismay; 1950) have indicated that P.A.S., in the form administered, is potentially hepato-toxic.

The case here reported is of a patient who developed a most profound systemic reaction following the administration of sodium P.A.S. and streptomycin, with exfoliative dermatitis, liver and kidney damage, and an intense bone-marrow response. Later she had a reaction to penicillin.

Case Record

A single woman aged 23 was admitted to hospital on January 25, 1950, with a cavity at the right apex; sputum positive. Thoracoplasty was recommended, but before it could be carried out the disease spread to the right mid-zone. To control this streptomycin (1 g. daily) and sodium P.A.S. (18 g. daily in divided doses) was begun on March 24.

Stage 1 (April 13–19): Prodromal Symptoms.—On April 13 the temperature rose suddenly to 100° F. (37.8° C.) and slight headache ensued. Both drugs were continued, as other patients had had similar reactions, which settled in a day or two. Temperature fell to 99° F. (37.2° C.) and patient felt better. On April 19 the leucocytes numbered 6,100 (eosinophils 10%).

Stage 2 (April 20–28): Exfoliative Dermatitis.—On April 20, after 27.5 g. streptomycin and 504 g. P.A.S., patient complained of nausea, dyspnoea, and pain in right side of chest. Temperature rose to 101.4° F. (38.6° C.). Next day she had a rigor and vomited; temperature 103.4° F. (39.7° C.). An intensely irritating maculo-papular rash appeared on the abdomen and rapidly became generalized, affecting particularly extensor surfaces of the forearms and legs, where it soon became vesicular and later haemorrhagic. Face swollen and puffy; glands in posterior triangle enlarged and tender. Tongue and inside of mouth became ulcerated; swallowing, even of fluids, was exceedingly difficult and painful. Motions were loose (no pathogens isolated); urinary output fell to 15 oz. (425 ml.) a day. Leucocytes numbered 44,000 (eosinophils 19%) on April 25, and 70,000 (eosinophils 19%) on