to normal within about 10 days after withdrawing therapy. The authors state that there is indirect evidence which indicated that the defect involves the hepatic excretory mechanism rather than the liver dye uptake.

It has also been shown that 30 mg. daily of norethandrolone for six weeks given to six laboratory workers produced a consistent and significant increase in the level of serum glutamic-oxalacetic transaminase, serum lactic dehydrogenase, and serum aldolase, and a marked retention of bromsulphthalein in all subjects. There was no change in thymol turbidity and cephalin flocculation tests and no jaundice (Dowben, 1958).

Conclusion

Although jaundice is a rare complication after methyltestosterone, there is apparently no evidence of liver-cell damage, and recovery of liver function follows its withdrawal. Because of the comparative rarity of this complication and its apparent transient character, we do not feel that there is enough evidence to justify withholding therapy with methyltestosterone, especially in view of its simplicity and efficiency as an oral androgenic and anabolic substance. It is prudent not to give this steroid again to a patient who has developed cholostatic jaundice during a previous course.

We are indebted to Drs. Fearnley, Tomlinson and Balmforth, Hanger, Higgins, Hirsch, Nabarro, Oleesky and Munro, Oliver, Palmer, Priest, Skillern, Taverner, and Westlake for supplying details of further cases in response to our request, and for allowing us to incorporate them in this paper; to Dr. G. R. Venning, of Searle Research Laboratories, for information about norethandrolone jaundice; and to Professor Sir Roy Cameron and Dr. Sheila Sherlock for their helpful criticism.

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CHRONIC BRONCHITIS IN INDUSTRY

AN ACCOUNT OF A TRIAL OF H. INFLUENZAE VACCINE

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Chronic bronchitis is roughly five times as common in Britain as in most industrial European countries and ten times more so than in Scandinavia or the United States. Economically the cost in lost working days, production, and health insurance claims is tremendous (Stuart-Harris and Hanley, 1957).

It is difficult to account for this high prevalence, although numerous predisposing factors such as age, heredity, sex, climate, atmospheric pollution, and smoking have been indicted (Oswald *et al.*, 1953). There is wide agreement that bronchial infection is of paramount importance, particularly in determining whether the disease progresses to the disabling irreversible stage (Ogilvie and Newell, 1957).

Attention has therefore been concentrated upon the infective aspect, especially as Mulder (1938), Mulder and Goslings (1948), and May (1953a, 1953b, 1954) have demonstrated that *Haemophilus influenzae* can be found in the sputum of up to 90% of chronic bronchitics. The pneumococcus comes next in frequency. Other pathogens are relatively uncommon. These organisms are rapidly reduced in number by treatment with suitable antibiotics, but they promptly re-establish themselves afterwards (May, 1953b).

Elmes *et al.* (1953) found short courses of various antibiotics only slightly and transiently effective, but they subsequently reported considerable benefit from a

week's course of oxytetracycline given at the onset of an exacerbation of infection (Elmes *et al.*, 1957). Others have tried long-term tetracyclines prophylactically (Finke, 1954; Helm *et al.*, 1956; Moyes and Kershaw, 1957), but side-effects, expense, the risk of super-infection, and, as Naish (1957) pointed out, the danger of spreading antibiotic-resistant organisms through the community constitute serious objections to this type of therapy.

This unsatisfactory situation has led to further consideration of the immunological state of the bronchitic harbouring *H. influenzae*. It has been found by May (personal communication, 1956) and by Nicol Roe (1957, personal communication) and confirmed in the present investigation that many chronic bronchitics show briskly positive skin reaction to *H. influenzae* antigens, suggesting that they are in a state of hypersensitivity. Although the exact relationship between this organism and the bronchitic process is still not clearly defined, it seems reasonable to postulate that hypersensitivity might play a part in the inflammatory reaction characteristic of the disease.

The possibility thus arises that these patients might benefit from a graded course of *H. influenzae* vaccine, the object being to desensitize rather than to immunize them. With this in mind Edwards *et al.* (1957) used an autogenous *H. influenzae* vaccine along with oxytetracycline or a sulphonamide, but the result was negative.

We now report a larger trial designed to assess the value of a specially prepared stock *H. influenzae* vaccine in two industrial populations.

Organization of Trial

At the end of October, 1957, the management of the Stanton Ironworks Company Limited approved a trial of *H. influenzae* vaccine at (*a*) Stanton Ironworks, near Nottingham, employing 5,600 men, with a whole-time medical officer, visiting consultant chest physician, and *x*-ray apparatus; and (*b*) Holwell Ironworks, near Melton Mowbray, employing 1,600 men and visited by the doctor from Stanton.

"Men with winter coughs and bronchitis" were invited to volunteer "for a course of injections or tablets which, it is hoped, will reduce the amount of chest trouble they experience during the coming winter." The rather odd wording of this appeal was due to our knowledge that many men attribute their symptoms to smoking or environmental conditions and deeply resent any suggestions that they have bronchitis.

In the interests of speed, volunteers were merely interviewed singly or in groups at this stage so as to exclude those who had had antibiotics during the preceding two months and any with negligible symptoms. Unfortunately several genuine cases had been given antibiotics in the recent epidemic of Asian influenza.

Criteria for Diagnosis

In order adequately to evaluate the benefit derived from the vaccine it was necessary to know the relative numbers of severe, mild, and non-bronchitics in the group. As the trial proceeded each man was studied from various standpoints.

History

The following definitions of chronic bronchitis have been given. (1) Higgins *et al.* (1956): "The constant production of phlegm and one or more chest illnesses during the past three years." This implies confinement to the house, which means absence from work unless the illness occurs during a holiday or off-duty period. We feel that absence from work with chronic bronchitis depends upon the patient's social and economic circumstances, his means of transport, the type of work he does, and the therapeutic preferences of his doctor, even more than on his medical condition.

(2) Ogilvie and Newell (1957): "Cough with sputum, persistent through the winter or throughout the year, in the absence of other causative respiratory disease. A minimum duration of two years."

(3) Stuart-Harris and Hanley (1957) and Oswald (1958) regard breathlessness as important. We feel that this definition is too strict, because as a rule the condition is in an advanced and irreversible stage by the time the patient is referred to a chest clinic. Many men tolerate cough and sputum for years without seeking advice, even if they are attending their general practitioner for other reasons. Sometimes those with minimal symptoms have maximal disease as judged by radiographs and lung-function tests.

Table I shows the influence of these criteria on diagnosis.

TABLE I.—*Diagnosis of Bronchitis by Different Standards (Based Upon Answers to Questionaries)*

Standard Adopted	Stanton Ironworks		Holwell Ironworks		Total	
	No.	%	No.	%	No.	%
Ogilvie only ..	69	30·7	32	31·4	101	30·9
Higgins+Ogilvie	120	53·3	51	50	171	52·3
Not bronchitis ..	36	16·0	19	18·6	55	16·8
Total ..	225	100·0	102	100	327	100

This table refers only to those volunteers whose questionaries were completed.

Questionaries were completed by one observer (R. N. W.) for all volunteers except a few who had already been excluded and some who could not understand English. Questions related to cough, sputum, the duration of symptoms, wheeze, chest illnesses, dyspnoea, the effects of weather, colds "going down to the chest," nasal catarrh, and smoking (Table II). The following points are of particular interest.

TABLE II.—*Prevalence of Respiratory Symptoms—Stanton and Holwell Combined (Duration of Symptoms not considered)*

Age Group	No. in Each Age Group	No Symptoms	Chest Illnesses		Cough		Sputum		Cough and Sputum		Yellow Sputum		Wheeze		Breathlessness	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
15–	8	—	5	62·5	5	62·5	4	50	4	50	3	37·5	3	37·5	3	37·5
25–	66	—	39	59·1	56	84·8	56	84·8	51	77·2	43	65·2	45	68·2	9	13·6
35–	96	—	58	60·4	88	91·7	82	85·5	80	83·3	55	57·3	75	78·1	21	21·9
45–	88	—	59	67	88	100	80	90·9	75	85·2	50	56·8	79	89·8	31	35·4
55–	62	—	37	59·7	60	96·8	57	91·9	57	91·9	35	56·5	52	83·9	31	50
65+	8	—	7	87·5	8	100	8	100	8	100	3	37·5	8	100	4	50
Total	328	—	205	62·2	305	93	287	84·4	275	83·8	189	57·6	262	79·9	99	30·8

Presence of Cough and Sputum.—Many volunteers had difficulty in giving a straight "Yes" or "No" in answer to questions. Some men with sputum never cough, merely "hawking the phlegm up." Others in dusty occupations only have symptoms whilst at work.

Duration of Cough and Sputum.—Where symptoms had existed for less than three years the duration given by the volunteers was probably accurate. Beyond three years most volunteers had only a very vague idea of the precise year of onset, except where it could be related to the date of their demobilization from the Forces. For this reason the duration was usually entered in multiples of five years.

Wheezing.—So many men obviously failed to understand the meaning of "wheeze" that this question appeared valueless.

Chest Illnesses.—Volunteers were asked how many chest illnesses they had had in the last three years which had kept them in bed, off work, or indoors. For this purpose "'flu" was regarded as a chest complaint. At Holwell Ironworks an attempt was made to cross-check these histories with the absentee cards in the Labour Office. After making due allowance for discrepancies attributable to an inadequate diagnosis (such as "illness") and illnesses which occurred in off-duty periods it was reckoned that in 72 of 101 cases the history of chest illnesses given by the volunteer was reasonably accurate, in 23 cases the duration or frequency of the spells of absence had been overstated, and in six cases it had been underestimated.

Dyspnoea.—Of the five grades of dyspnoea adopted by the Pneumoconiosis Research Unit only grades 2, 3, and 4 were utilized (Table III) (grade 1 relates to dyspnoea only on severe exertion, and grade 5 to such severe dyspnoea that the patient cannot come to work).

TABLE III.—*Prevalence of Dyspnoea in Different Degrees of Bronchitis*

Standard Adopted	No Dyspnoea		Grade 2		Grade 3		Grade 4		Total
	No.	%	No.	%	No.	%	No.	%	
Ogilvie	77	76·2	17	16·8	3	3	4	4	101
Higgins + Ogilvie	108	63·2	31	18·1	25	14·6	7	4·1	171
Not bronchitis	43	78·2	10	18·2	—	—	2	3·6	55

Smoking Habits.—29 men (9.1%) had not smoked within the previous 15 years; 130 (40.5%) had changed their smoking habits significantly during that period.

Clinical Signs

Owing to the unreliability of clinical signs volunteers were not examined.

Radiological Appearances

100-mm. chest radiographs were taken of all volunteers at Stanton Ironworks. At Holwell Ironworks recruitment was limited to those who had been examined a few weeks earlier by the mobile mass radiography unit. The group therefore included no cases of active tuberculosis or carcinoma, but it is possible that a few men had asthma or bronchiectasis.

Simon (1956) attempted to place the radiographical diagnosis of emphysema on a sound scientific basis by insisting upon changes in the appearances of the diaphragm and cardiovascular structures and possibly the presence of bullae. In our opinion this is too strict. The chest physician has the advantage over the radiologist in that by both examining the patient and interpreting his film he gradually comes to know the appearances which fit with the clinical findings of emphysema. On the other hand, there is the danger of reading the film with a mind already prejudiced by the results of physical examination. Bias acquired in this way cannot reasonably be said to apply when, as in this trial, the films were read without examining the patients. The main radiological criteria of emphysema which we adopted were first and foremost the pattern of the lung markings, the recognition of which is largely subjective and a matter of experience, then the shape of the thoracic cage, diaphragm, and heart, as described by Simon.

Blind re-scrutiny of all 100-mm. films at the end of the trial demonstrated that radiological diagnosis was reliable in the severe cases, but not in milder degrees of emphysema.

Lung-function Tests

Ventilatory capacity was measured by recording the volume of air expelled in the first 0.75 second of a forced expiration, using a modified Gaensler apparatus. The mean of three readings was taken in the standing posture after two practice attempts.

TABLE IV.—*Indirect M.B.C. (litres/minute) and Sitting Height*

Age (Years)	No. in Group	Mean M.B.C.	Mean Sitting Height
15–	7	145	36½ in. (92 cm.)
25–	66	126·6	35½ ,, (90 ,,)
35–	84	108·3	35¼ ,, (89·5 ,,)
45–	88	92·3	35 ,, (89 ,,)
55–	59	71·8	33¼ ,, (84·5 ,,)
65+	6	62·5	34½ ,, (87·5 ,,)

TABLE V.—*Relation of Grade of Dyspnoea to Indirect M.B.C.*

Grade of Dyspnoea	No. in Group	Mean Indirect M.B.C.
2	58	77
3	28	60·5
4	13	52·5

Results have been expressed in litres/minute as the indirect maximum breathing capacity (indirect M.B.C.). Table IV shows the steady decline in ventilatory capacity with age. In the 55–64 age group 15 (25.4%) had a reading of less than 50 litres a minute. Table V shows that increasing dyspnoea is matched by a reduction in the mean indirect M.B.C., but except in advanced cases there was no correlation between the indirect M.B.C. and the appearance of the chest *x*-ray film.

Classification of Volunteers

On the results of the questionary volunteers were classified according to the definitions given (Table I).

It will be seen that, taking the two works together, 55 (16.8%) of the volunteers were not bronchitic, 101 (30.9%) satisfied Ogilvie's criteria, and the remaining 171 (52.3%) satisfied both Ogilvie's and the stricter criteria of Higgins. *X*-ray findings confirmed the diagnosis in about half the cases at Stanton.

The "non-bronchitics" all had symptoms of some kind, but these were either too mild or of too short a duration.

Composition of the Group

Volunteers included all grades of management, skilled and unskilled workers employed in the company's coke ovens, blast furnaces, foundries, concrete plants, farms, transport department, and offices. The results should not therefore be taken as typical of any particular occupation or social class. Ages ranged from 17 to 71 years.

Preliminary Investigations

Skin Sensitivity Tests.—These were performed and read by the medical officer or State-registered nurses in mid-December. 0.05 ml. of *H. influenzae* antigen,

0.05 ml. of a control, and 0.05 ml. of mixed antigen were injected intradermally in the forearm. As this was done at work the result had to be observed next day. A positive reaction was regarded as one with an area of erythema exceeding 10 mm. in diameter; anything less was negative. As shown in Table VI 79.3% of volunteers had positive reactions to *H. influenzae* at Stanton and 79.6% at Holwell.

TABLE VI.—*Result of Initial Skin Sensitivity Tests*

	Stanton Ironworks		Holwell Ironworks		Total	
	No.	%	No.	%	No.	%
Positive to *H. influenzae* only	152	65·5	60	58·3	212	63·3
Positive to mixed antigen only ..	2	0·9	1	0·9	3	0·9
Positive to both	32	13·8	22	21·3	54	16·1
Negative to both	46	19·8	20	19·4	66	19·7
Total ..	232		103		335	

Agglutination Titres.—Samples of venous blood were taken from about 10% of volunteers and titrated against a standard *H. influenzae* cell suspension. The results showed the dilution of serum which would just cause agglutination of the test organism.

Sputum Smears.—One specimen of morning sputum was requested from each volunteer. They were stained by Gram's method in parallel with smears of sputum from healthy individuals to which *H. influenzae* cells (from cultures) had been added. The latter served as identification standards. *H. influenzae* was found in 24.9% of samples.

Courses of Treatment

After the skin-sensitivity tests had been read alternate volunteers were allocated to injection or control groups. As it was considered ethically unjustifiable to subject half the volunteers to a strenuous course of useless injections the control group was given tablets containing 3 mg. of aneurine hydrochloride in bottles labelled "special vitamin tablets. One to be taken every morning."

The *H. influenzae* vaccine contained 1,000 million bacterial cells per ml. The dose depended upon the skin sensitivity tests. Where there had been a positive response to *H. influenzae* the dose schedule was: 0.2, 0.4, 0.6, and 1 ml. twice weekly, then 1 ml. monthly until March. Negative reactors were given 0.4, 0.6, and 1 ml. twice a week, then 1 ml. monthly until March.

The trial was stopped at the end of March. Skin-sensitivity and blood tests were repeated. Specimens of sputum were sought from those with *H. influenzae* in their original specimen and from a number of others.

Results

Cases Withdrawn from the Trial.—Volunteers were withdrawn if they received antibiotics for any reason (18 cases), were absent so long as to interfere with the course (9 cases), or left the company (6 cases). Twelve volunteers withdrew at their own request because of the alleged ill effects of vaccine or tablets. Three others were withdrawn for various reasons.

Alleged Ill Effects of Treatment.—Of the four in the tablet group who withdrew because of alleged ill effects one complained that the tablets made his chest so tight that he could hardly breathe; the others had general complaints such as headache. A few men remarked that the tablets had made them gain weight. Eight men receiving vaccine withdrew because of painful reactions at the site of injection or influenza-like symptoms. Of those who survived the full course of injections, 30% admitted having ill effects. About half of them complained of local pain or swelling, whilst the other half had had "slight attacks of 'flu" or the symptoms of a severe cold lasting up to 36 hours after injections. There was no significant difference between the effects of a commencing dose of 0.2 ml. and one of 0.4 ml.

Subjective Improvement.—All remaining volunteers were asked whether the course of treatment had been worth the effort involved. Care was taken to point out to them that we were primarily concerned with cough and sputum, not with the incidence of colds. Those who reported only a slight improvement, or very doubtful benefit, were classed as "not improved." Taking the volunteers as a whole—regardless of their degree of bronchitis—116 (76.7%) of 151 in the injection group felt that the treatment had been well worth while, compared with 101 (73.2%) of 138 in the tablet group. This suggests that a large number of people respond to careful individual consideration of their cases, regardless of the remedy. In both groups there were some men who reported really dramatic amelioration of symptoms, as demonstrated by their ability to take part in dances or to walk to work in deep snow. Several volunteers requested further supplies of tablets or another course of injections next winter. The results in men with undoubted bronchitis as diagnosed by questionaries, lung-function tests, and radiographs showed no difference from those of the volunteers as a whole. Some men who reported improvement following injections subsequently said that their condition deteriorated two or three weeks after the end of the course.

Loss of Working Time.—At the end of the trial the absentee cards of all volunteers who had reported a chest illness in the preceding three years were reviewed to see how many spells of absence had occurred in January, February, and March, 1958. It was found that there was no significant difference between the injection and tablet groups at either works (Table VII).

TABLE VII.—*Effect of Treatment on Absence Due to Chest Illnesses*

Standard of Bronchitis Adopted	Injection Group		Tablet Group	
	No. in Group who had a Chest Illness in Preceding 3 Years	No. of these Men who Survived Trial Period without Chest Illness	No. in Group who had a Chest Illness in Preceding 3 Years	No. of these Men who Survived Trial Period without Chest Illness
Higgins+Ogilvie	84	68 (80·9%)	60	49 (81·7%)
Not bronchitis ..	12	8 (66·6%)	23	19 (82·6%)

Radiographs.—It was assumed that no radiological improvement would be observed, so radiographs were not repeated at the end of the trial.

Lung Function Tests.—There was no correlation in either group between changes in ventilatory capacity and subjective improvement or deterioration. Of volunteers tested at the beginning and end of the trial, 7.2% rose by more than 10% and 17.9% fell by more than this amount.

Clearance of H. influenzae from Sputum.—The course of injections was no more effective than the tablets in clearing *H. influenzae* from the sputum. Of the 47 cases in which *H. influenzae* was present at the start of trial the examination was repeated in 38, of whom 32 showed no *H. influenzae* at the second test.

Alteration in Agglutination Titres.—There was a tendency for titres to fall in both the injection and control groups. This supports the report of Faunce

(quoted by Oswald, 1958) that autogenous vaccines did not influence the titres in a small series of cases. Of the 21 men from whom blood was taken on both occasions only one did not report any benefit. He had received injections and his agglutination titre had fallen from 1/160 to <1/10.

Alteration in Skin-sensitivity Reaction.—There was no significant change in either group.

If volunteers are considered according to their degree of bronchitis it is found that the proportion of non-bronchitics with a positive response to *H. influenzae* at the first test is 48 out of 56 (85.7%) compared with 79.6% in volunteers as a whole. This confirms the findings of May and Faunce (1958, personal communication) who, using a phenol-killed suspension of *H. influenzae*, found many positive reactors among non-bronchitics.

Discussion

The late start to this trial was unfortunate in that not only were a large number of genuine cases unacceptable because of antibiotics administered during the epidemic of Asian influenza, but some others had begun their annual prophylactic course of antibiotics. Obviously any attempts to desensitize patients to *H. influenzae* should be completed by September, before the autumn and winter recrudescences occur.

When subjected to closer study the trial groups were found to contain many with mild symptoms. It was not possible to undertake a comprehensive investigation on account of the numbers involved. A more intensive study of a small group of severe cases, including complete clinical sputum and electrocardiographic examinations, might have been more profitable, and the bacteriological and immunological data obtained might have helped to elucidate the role of *H. influenzae* in chronic bronchitis.

The amazing co-operation and perseverance shown by the volunteers, in spite of a high percentage of minor ill effects, was the most outstanding feature of the trial, and demonstrates very clearly the working-man's fear of bronchitis and his willingness to undergo any attempt at prophylaxis—with the notable exception of attempts to convince him of the evils of cigarette smoking.

The dosage of vaccine used was arbitrarily chosen because of lack of previous experience, but the frequency of minor ill effects indicates that this dosage is about the upper limit of this particular preparation that could be tolerated.

Assessment of results was rendered difficult by the lack of any satisfactory criterion of improvement. Subjective assessments were unreliable, as shown by the improvement claimed by the control group. Absenteeism might have been more helpful under more favourable circumstances. The only yardstick available was the indirect M.B.C., which not surprisingly showed no advantage for the vaccine.

Even when all the unsatisfactory features of the trial are taken into account it would appear that, in a sample of this size, some advantage should have been demonstrated if the vaccine had been able to give any useful degree of protection against exacerbations of chronic bronchitis.

Summary

A trial is reported of injections of a specially prepared *H. influenzae* vaccine in a group of male factory workers, with a view to reducing the incidence of relapses of chronic bronchitis during the first three months of 1958. No evidence was gained to suggest that the injections conferred any benefit as compared with a corresponding number of control patients.

It is suggested that, for the present, trials should be confined to small groups of carefully investigated subjects, so that the effect of such vaccines may be related more closely to changes in pathological findings and clinical condition.

We thank the managing director of the Stanton Ironworks Company Ltd. for permission to carry out the trial and publish the paper, the employees of the company for volunteering, the Medical Department staff for the additional work involved, and the Medical Department of Messrs. Glaxo Laboratories Ltd. for supplying materials, providing guidance, and carrying out pathological investigations. We would also thank the local general practitioners for their whole-hearted co-operation.

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SARCOIDOSIS OF THE NERVOUS SYSTEM

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Involvement of the nervous system by sarcoidosis is now recognized with increasing frequency. Despite great variation in the symptoms and signs many cases present a recognizable clinical syndrome. It is the purpose of this paper to describe three further cases, to stress the features they showed in common, and to attempt an assessment of the results of steroid therapy.

Case 1

A married woman of 35 was admitted to hospital on June 1, 1954, under the care of Dr. D. V. Hubble. Her illness had begun four months earlier with pain in the lumbar region, soon spreading to the dorsal spine and neck. The pain appeared to be relieved after massage, but she then developed sensations of numbness in the left thigh, the whole of the right lower limb, and both upper limbs. The left upper limb felt weak and she experienced tingling in the right side of the face, later spreading to the left. These symptoms were severe for about two weeks and then improved. Six weeks before admission she developed swellings of both cheeks that subsided in a week. The right side of the face became weak and a few days later she lost her sense of taste and of smell. As these symptoms also improved she developed difficulty in swallowing and for two weeks could take no solid food. She remarked that her tongue felt like wood and was difficult to move. Two weeks before admission she was swallowing normally but