Patients given chlorpromazine = blood sugar mean was 62 and fell 73-62=11 mg. per 100 ml.

Therefore chlorpromazine has no significant effect on the prolonged fall of blood sugar following a dose of insulin.

Therefore chlorpromazine has no significant effect on fasting blood-sugar level (slight hypoglycaemic effects may later be revealed on a large-scale investigation), on immediate fall in blood-sugar level following a dose of insulin, or on prolonged fall in blood-sugar level following a dose of insulin.

Combined Effects

The combination of insulin with chlorpromazine had a marked effect both on the subjective feelings and on the behaviour of the patient. Subjectively, the patient experienced migrainous headaches, dizziness, palpitation, and drowsiness, but no spontaneous complaint was made of these symptoms during the hours of treatment—that is, 9.30 a.m. to 12.30 p.m. These symptoms could be elicited either by direct questioning during the treatment or else the patient would mention them spontaneously later in the day after the effects of the drugs had diminished.

The behaviour of the patients followed a definite pattern and they became motionless, drowsy, and relaxed. This state appeared to be very similar to that which can be produced by light hypnosis. The excited refractory patients were appreciably calmer and more manageable when on combined insulin and chlorpromazine than when on chlorpromazine alone. Feeding difficulties and the loss of weight, neither of which had been relieved by the chlorpromazine alone, disappeared with the combination.

No evidence of any liver damage was obtained with the patients on the combination, though a transient jaundice, which faded when the drug was stopped, appeared in one of the patients on chlorpromazine alone. There was no evidence of chlorpromazine decreasing the predisposition to epileptic fits which sometimes occurs with hypoglycaemia. In fact, the clinical impression was of some slight increase in this tendency.

Conclusion

Chlorpromazine did not influence the action of insulin on blood-sugar levels. There was slight apparent lowering of fasting blood-sugar levels, but this was not statistically significant.

Chlorpromazine caused some apparent but not significant decrease in the total number of anxiety symptoms and altered the type of these symptoms. Palpitation and tachycardia were increased. Perspiration, flushing, anxiety, restlessness, epigastric sensations, and tremor were diminished.

Insulin and chlorpromazine combinations were useful in controlling refractory excited patients who were not controlled by either chlorpromazine or insulin alone in the above dosage.

The combination was also useful in making more manageable patients who became excited during insulin coma treatment. When chlorpromazine (100 mg. orally) was given along with the insulin and (50 mg.) later in the day, there was such a marked diminution in restlessness and excitement that schizophrenic patients who were previously unmanageable and had to have their treatment discontinued were enabled to be given a full course of comas. No difficulty was experienced in terminating the comas by the usual methods, and doses of insulin up to 670 units have been used in combination with the chlorpromazine.

Owing to the possibility of the lethargic, stuporous state deepening into hypoglycaemic coma, adequate nursing supervision and arrangements for giving emergency glucose are needed.

One complication of chlorpromazine is liver damage (Lehmann and Hanrahan, 1954). The insulin should help to protect damage of the liver by promoting glycogenesis.

The comments of one of the patients on chlorpromazine, 100 mg. at 9 a.m., and insulin, 20 units at 9.30 a.m., are worth recording. "I haven't noticed very much difference.

I got throbbing headaches about 10.30 a.m. and palpitations about 11 a.m. When I had been on tablets (chlorpromazine) alone my legs felt weak. On injections (insulin) and tablets (chlorpromazine) I felt tired and wanted to sleep. Sleep was not thoroughly deep because my mind was still on the turn. Time passed quickly. Directly after the treatment (12 a.m.), for two hours I felt very confident. I could go to the canteen without the feeling that people were looking at me. It was a beautiful feeling—just the opposite feeling to what I usually get. The confident feeling wears off, and by tea-time I am wary. I wonder whether to chat at table or to say nothing. At lunch I can eat a lot and make a pig of myself and not care. At tea it is different, and I am self-conscious again. The treatment has not eradicated anything from my mind. I know it is still up to me to face my difficulties."

Summary

A total of 31 patients were given combinations of chlorpromazine and insulin. The blood-sugar levels in 19 patients and the symptoms induced by insulin in 11 patients were compared both before and after chlorpromazine had been given.

The effect of insulin and chlorpromazine combined as a means of therapy was compared with the effect of each of these compounds used separately.

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AIR POLLUTION AND BRONCHITIS

BY

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The crude death rate from bronchitis shows a steady and marked increase in passing from rural areas to the towns, cities, and conurbations (Table I). Attention has recently been directed to air pollution as a possible

TABLE I.—Death Rates from Bronchitis (International List Nos. 500-502) Per 100,000 Living, by Population Density, England and Wales, 1951

		Rural Areas	Urban Areas			Conurbations
			Less than 50,000	50,000 to 99,999	100,000 and over	
Population (thousands)	M. F.	4,276 4,166	4,477 4,868	1,583 1,753	2,761 3,030	7,952 8,934
Bronchitis death rates per 100,000	M. F.	69.4 47.3	98.5 56.0	100 58.5	117.8 64.9	132.1 73.7

cause for some of these differences, and the great increase in deaths, most notably from bronchitis, which occurred during and immediately after a prolonged smoke fog in London in 1952 (Logan, 1953) has added

weight to this hypothesis. The fatal effects of severe smoke fogs have been described on several previous occasions (Marsh, 1948; Schrenk *et al.*, 1949; Logan, 1949; County M.O.H. for London, 1952). The victims are usually, though not invariably, adults in the latter half of life or sufferers from chronic respiratory disease. The illness from which they die appears typically to be in the nature of an acute suffocative bronchiolitis.

We do not know to what extent, if at all, air pollution of a lesser degree than that which causes these dramatic episodes is harmful to health. One way of examining this question is to see to what extent death rates vary with the average air pollution in different localities. An attempt has been made to do this for the county boroughs of England and Wales for bronchitis in relation to air pollution with sulphur dioxide and with solid matter. Sulphur dioxide has fallen under suspicion because it has been shown in the laboratory to have effects on human respiratory function in concentrations met with in smoke fogs; Amdur *et al.* (1953) found that the inhalation of sulphur dioxide in concentrations of 1-8 p.p.m. increased the pulse and respiratory rates in normal human volunteers and caused the respiration to become more shallow. Cralley (1942) showed that sulphur dioxide in concentrations somewhat higher than those encountered in smoke fogs inhibited ciliary activity in the human trachea.

Present Investigation

Two age groups were selected for this study, 45-64 and 65+, as it is at these ages that bronchitis is commonest and susceptibility to smoke fogs greatest. The numbers of deaths and the populations at these ages were obtained from the Registrar-General's Annual Review and the 1951 census

FIG. 1.—Relationship between bronchitis death rates in 35 county boroughs and mean sulphur dioxide air pollution. Men aged 45-64, 1951. Correlation coefficient=0.5076. Significant between 0.1 and 1%.

FIG. 2.—Relationship between bronchitis death rates in 35 county boroughs and mean sulphur dioxide air pollution. Men aged 65+, 1951. Correlation coefficient=0.4443. Significant between 1 and 2%.

1% sample respectively. From these figures the bronchitis death rates in the different county boroughs were calculated. The air pollution records were taken from the atmospheric pollution bulletins published monthly by the Department of Scientific and Industrial Research. All the county boroughs in England and Wales making returns of monthly readings from two or more stations (lead peroxide candle method) were used.

The existing air pollution data when used as a measure of the quality of the air inhaled by the population of a county borough suffers from certain deficiencies. Stations have not always been sited to record average conditions, but have sometimes been placed in specially chosen situations in order to pin-point a particularly bad area. Prevailing winds and geographical configurations influence the readings, and the number of stations in proportion to population varies from one county borough to another.

In the first instance, the mean of the maximum monthly readings (amongst the different stations) for each county borough was used as a yearly index. Later it was found that a similar result was obtained if all the stations in each county borough were included in calculating the mean annual figure. The latter was then adopted as the index. Scatter diagrams relating the death rates from bronchitis to the mean annual sulphur dioxide pollution figure were constructed for men and women in the two age groups (45-64 and 65+) for the years 1950, 1951, and 1952—that is, for the census year and the years on either side of it. Figs. 1 and 2 show the diagrams for the men for 1951 and illustrate the relationship between bronchitis death rates and sulphur dioxide pollution that was found to occur in both male age groups for all three years. Correlation co-efficients were calculated. In the men there was a moderate degree of correlation in each case, and the likelihood that this association was due to chance varied from 1 in 50 to 1 in 1,000 (Table II). In the women, on the other hand, in only two out of the six sets of data was there a significant association—namely, in women over 65 for the two years 1951 and 1952.

Although there is a significant statistical association between bronchitis death rates in men over the age of 45 and sulphur dioxide pollution, it is clear that this association might be due to both variables being directly related to a third variable or group of variables. The possibility that immediately springs to mind is that both might be related

TABLE II.—*Correlation Coefficients Between SO₂ Air Pollution and Bronchitis Death Rates in 33-35 County Boroughs*

Age	1950			1951			1952		
	τ	No.	Proba- bility	τ	No.	Proba- bility	τ	No.	Proba- bility
Men:									
45-64	0.5478	33	Sig. 0.1 to 1%	0.5076	35	Sig. 1 to 2%	0.4613	35	Sig. 0.1 to 1%
65 +	0.4513	33	Sig. 0.1 to 1%	0.4443	35	Sig. 1 to 2%	0.4095	35	Sig. 1 to 2%
Women:									
45-64	0.2732	33	Not sig.	0.2763	34	Not sig.	0.2932	34	Not sig.
65 +	0.3378	33	"	0.4279	35	Sig. 1 to 2%	0.6223	35	Sig. 0.1%

to the complex of general social conditions or to some component of it. Indeed, the Registrar-General's Decennial Supplements (1938, 1954) show clearly that in both sexes there is a strong relationship between the standardized mortality ratio for bronchitis and social class as defined on an occupational classification. If sulphur dioxide air pollution showed a similar relationship to general social conditions, then the significance of the association between bronchitis deaths and sulphur dioxide pollution would be reduced.

This possibility was tested by using two separate indices of social conditions and relating them to the mean sulphur dioxide pollution figures. The first index was the average number of persons per room in the different county boroughs as given in the 1951 census 1% sample report (Registrar-General, 1952), and the second was a social class of towns scale devised by Wilkins (1952) and based on the estimated percentage of households in which the chief wage earner's basic weekly wage rate equalled or exceeded £7 10s. The same county boroughs were used in all three cases.

The correlation coefficient between persons per room and sulphur dioxide air pollution was -0.1538 and between the income classification and sulphur dioxide pollution -0.2478. In neither case was this slight degree of association statistically significant.

Bronchitis and Other Pollutants

It seemed possible that bronchitis death rates might be related not specifically to sulphur dioxide pollution but to some other pollutant, the amount of which in the air varied with the amount of sulphur dioxide, or to a combination of pollutants.

The Committee on Air Pollution (1953) estimated the amount of the chief pollutants discharged annually in Great Britain as follows:

Smoke	..	..	..	2.1 million tons
Grit	..	..	..	0.6 " "
Sulphur dioxide	..	..	..	5.3 " "
Other acids (nitric and hydrochloric)	..	..	..	0.3 " "
Carbon monoxide	..	..	..	24.0 " "

Most of the pollution stations record total solid matter deposited in addition to sulphur dioxide. The same procedure was adopted as in the case of sulphur dioxide to see if there was any statistical relationship between bronchitis death rates and solid matter pollution. Table III shows that

TABLE III.—*Correlation Coefficients Between "Total Solids" Air Pollution and Bronchitis Death Rates in 33-42 County Boroughs*

Age	1950			1951			1952		
	τ	No.	Proba- bility	τ	No.	Proba- bility	τ	No.	Proba- bility
Men:									
45-64	0.1727	40	Not sig.	0.4568	42	Sig. 0.1 to 1%	0.5439	33	Sig. 0.1 to 1%
65 +	0.2387	40	"	0.1863	42	Not sig.	0.5724	33	Sig. 0.1%
Women:									
45-64	0.2597	40	"	0.2232	42	"	0.3220	33	Sig. 5%
65 +	0.1299	40	"	0.1664	42	"	0.4601	33	Sig. 0.1 to 1%

there was a significant association between death rates from bronchitis and solid matter pollution for both sexes and in both age groups selected for 1952. However, in the eight sets of data relating to 1950 and 1951 only in one case (men aged 45-64, 1951) was there a significant association. It would appear, therefore, that there is a much stronger association between bronchitis mortality rates and sulphur dioxide pollution than there is between the former and air pollution with solid matter.

Discussion

It is difficult to draw any very firm conclusions based on the statistical approach because of the imperfections of the basic data. Bronchitis is a disease which, although very commonly diagnosed, is still not well defined or understood. The pollution records are unsatisfactory, as we cannot be confident, for the reasons given above, that they give a fair estimate of the amount of pollutants actually inhaled by the populations concerned. However, the consistency of the relationship between mean sulphur dioxide pollution and bronchitis death rates in the county boroughs does strongly suggest that whatever other factors may be involved sulphur dioxide pollution plays some part in causing death from bronchitis. From the limited data examined it would seem to be more important in this respect than pollution of the air with solid matter.

The general poverty complex has been shown to be of basic importance in determining the death rate from bronchitis (Registrar-General, 1938, 1954), but it appears from the calculations which have been made that air pollution can be separated from these as a distinct aetiological factor. W. Roe and R. Wrighton (1952, unpublished communication), using an index of social conditions in the county boroughs devised by Buckatzsch (1946), found that there was no relationship between bronchitis death rates and air pollution at ages under 15. The most likely hypothesis would seem to be that air pollution is not a prime aetiological factor in bronchitis but that it acts as a secondary or aggravating factor, and that on certain occasions, as in a prolonged smoke fog, it can have a fatal effect on those who are subject to this disease.

Much further research is required to establish the exact part that air pollution plays in the causation and aggravation of respiratory disease. In particular, morbidity studies are required in which the incidence of bronchitis and its exacerbations are studied in relation to variations in meteorological and pollution conditions.

Summary

A significant correlation has been found between the average sulphur dioxide air pollution in the county boroughs of England and Wales and the mortality rates for bronchitis in men aged 45 and over, for the three years 1950, 1951, and 1952. In only two of six sets of data was a similar association found for women at the same ages.

The association between air pollution with solid matter and bronchitis mortality rates was much less consistent. Only three of the six sets of data in the case of men and two in the case of women were significant.

There was no significant association between average sulphur dioxide pollution and two indices of general social conditions. The latter consisted of one based on income and one on housing conditions. The evidence supports the hypothesis that sulphur dioxide air pollution is a factor in determining the magnitude of the bronchitis death rate of middle-aged and elderly males.

Miss Audrey Hutcheson carried out the computations and prepared the diagrams for this study.

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THE COLLAGENOUS CHANGES IN THE INTERVERTEBRAL DISK WITH AGE AND THEIR EFFECT ON ITS ELASTICITY

AN X-RAY CRYSTALLOGRAPHIC STUDY

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The histological changes in the structure of the intervertebral disk throughout life have been well described by Coventry, Ghormley, and Kernohan (1945). These indicate that an integration process occurs during the first and second decades of life, but that in the third decade evidence of degenerative change appears. Little attention has been paid to the collagenous structure in the disk, and our work has been directed to this in an endeavour to elucidate changes in the collagen/mucopolysaccharide complex in the disk. The bearing of this work upon the aetiology of disk herniation is being studied at the present time and will be described in a later publication.

Our studies were made on fresh human intervertebral disks removed at operation or necropsy, using an x-ray

spectrometer with a comparatively high intensity x-ray beam. This allowed x-ray diffraction photographs of the specimens excised from the disks to be examined rapidly, so that little change in the structure of the material was possible during the exposure of approximately half an hour.

Experiments with Air-dried Specimens

The annulus fibrosus was peeled from the disk and cut into long strips which could be held in the clamps of a stretching frame for the investigation of the elasticity of the disk wall. The specimens of both nucleus and annulus were allowed to dry for ten hours to eliminate most of the unbound water, which, if present, produces an intense diffuse ring on the x-ray diffraction photographs of the material and so masks, to some extent, the x-ray diagram of the collagen or collagen/polysaccharide complex. If this process was allowed to continue too long, irreversible changes appeared in the structure of the collagen of the disk. In particular, specimens allowed to stand over several days showed changes in orientation, and the original structure could not be restored on wetting the sample again. Thus we think the specimens examined had a uniform moisture content during the course of the examination, and changes in crystallinity and orientation of the collagen were definitely related to the conditions of the material *in vivo*.

Our later experiments were made using a modified technique in that the disk was frozen and thin sections were then cut and mounted in the x-ray spectrometer. By this means the samples retained their swollen condition, as little water was dried out during the examination.

The collagen of the rat-tail tendon was used for comparison, and the following effect on its x-ray diagram was found on stretching: (a) increase in orientation of the fibrils, and (b) a reversible increase in the spacings associated with distances along the fibre axis comparable to the lattice extension of α keratin before the main $\alpha \rightarrow \beta$ transformation occurs (Table I).

TABLE I.—Reflections in X-ray Diagram of Rat-tail Tendon

Equatorial Reflections		Meridional Reflections		Other Reflections	
Unstretched	Stretched	Unstretched	Stretched	Unstretched	Stretched
11.8 Å	11.8 Å	2.86 Å	2.95 Å	7.2 Å	7.4 Å
5.7 Å	5.7 Å	3.95 Å	4.04 Å		
4.6 Å	4.6 Å				

A. Nuclear Changes with Age

Many specimens from subjects whose ages ranged from 3 weeks to 79 years were examined. The results of the x-ray diagrams are summarized in Table II (see Figs. 1-3).

The equatorial reflection at 11.8Å is associated with the side-chain spacing—that is, the average distance between the chains. It can be seen that this remains approximately constant in the air-dried specimens first investigated, except in those of an early age in which the reflection was absent.

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1.—Nucleus pulposus. Age 3 weeks (x-ray beam parallel to spinal axis). FIG. 2.—Nucleus pulposus. Age 48 years (x-ray beam parallel to spinal axis). FIG. 3.—Nucleus pulposus. Age 70 years (x-ray beam parallel to spinal axis). FIG. 4.—Annulus fibrosus. Age 2½ years (x-ray beam parallel to radial direction of disk).