TOXICITY OF SOME ATMOSPHERIC POLLUTANTS

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Examples of the harmful effects produced in man by contaminated fogs are now well known. The general clinical picture is one of respiratory embarrassment with increased dyspnoea, cyanosis, progressive cardiovascular embarrassment, and possibly fever and toxaemia if secondary infection occurs. It was similar in the London fogs of 1948 and 1952, in the Meuse Valley fog of 1930, and in the Donora incident in 1948. The young, the old, and those with pre-existing respiratory or cardiac disease are the more seriously affected, and the post-mortem findings are consistent with the inhalation of an irritant substance.

The nature of the irritant substance is still unknown, although various contaminants have been arraigned by different workers. Sulphur dioxide, carbon monoxide, automobile exhaust fumes, and fluorine compounds have been suggested (Firket, 1931; Roholm, 1937; Regan, 1953).

Unfortunately no lethal fog has been adequately sampled during the incident, nor have its chemical and physical properties been determined. It is therefore difficult to plan any experimental work on the toxic effects of polluted fog. The obvious contaminants must be studied first, but in the absence of precise knowledge of the possible concentration or the physical state of each substance in a smog the practical implications of the results obtained must be in doubt. Such a study will, however, indicate which contaminants are potentially dangerous and those which may be harmless, although synergistic effects may alter this simple classification.

We at Porton have examined effects on animals and human beings of various substances and mixtures which might be important atmospheric pollutants. The results of these experiments have been or are being reported in detail elsewhere, but it did seem desirable to summarize our progress to date and to consider the toxicological picture as a whole.

The use of animals must necessarily form part of such an investigation; the relative toxicities of possible contaminants and any synergistic effects can only be accurately determined by using subjects drawn from a homogeneous population, which cannot be obtained with human beings. In general most species of animals are less sensitive to these toxic pollutants than is the susceptible proportion of the human population.

Sulphur Dioxide

SO_2 is a pollutant commonly sampled in fog atmospheres. The concentrations reported in "smogs" (about 2 p.p.m. or less) have no detectable effect on any animal used. However, a small portion (perhaps 1/100) of human beings have been found to suffer from bronchoconstriction when inhaling low concentrations of this gas. In some cases slight tightness of the chest could be felt with concentrations as low as 1 p.p.m. In a London fog on January 5, 1956, one such subject experienced bronchoconstriction and severe respiratory distress, exactly similar to that produced by SO_2, when he attempted to hurry through the fog. In this instance the action of the gas was combined with the normal breathlessness due to exercise.

Smog atmospheres contain both SO_2 and smoke particles, and Meetham (1954) suggests that the SO_2 could be absorbed on to the smoke particles. It would then not be detected in the usual apparatus for measuring SO_2, as the air is filtered before entering the absorbent solution. Such SO_2–smoke particles would, however, if they existed, be inhaled and penetrate deeply into the lungs, and the SO_2 might be more toxic in this form than in the pure gaseous state.

The results of experiments on this subject have in some cases been expressed by the CtD_{50}. This is defined as the dosage (concentration time) to which a batch of animals has been exposed by the time 50% have died.

R. E. Pattle (unpublished results, 1955–6) has shown that the toxicity of SO_2 in a concentration of about 2,700 mg. per cubic metre (1,000 p.p.m.) to mice is enhanced by the addition of 100 mg. per cubic metre of smoke from a kerosene lamp. The CtD_{50} for the mixture was about 40% greater than that for the gas alone. In one experiment where the mean SO_2 concentration was the same (2,560–2,590 mg. per cubic metre) for the clean and the smoky atmospheres, at approximately 300 minutes (292–295 minutes) the mortalities were: clean atmosphere, 3/25; smoky atmosphere, 16/25. The final estimated CtD_{50}'s in the case last described were only in the proportion of 1 to 2.

The dosage of smoke administered in the above experiments is large and the higher mortality in the smoky atmosphere is not surprising. There is probably no need to postulate any interaction between smoke and SO_2 to account for the results. At necropsy the lungs showed intense congestion, areas of consolidation, collapse, and emphysema, and traces of oedema.

Previous exposure of mice to somewhat lower but still massive dosages of smoke (40 mg. per cubic metre for 22 hours) actually increases their resistance to subsequent exposure to SO_2 (*c.* 3,000 mg. per cubic metre; *c.* 1,000 p.p.m.). The ratio of the CtD_{50}'s for smoked to unsmoked mice was found to be 1.55, while after 200 minutes 20/49 unsmoked mice and only 6/49 of the pre-smoked group had died.

Other experiments have given similar results, so that it is undoubtedly a real effect. The cause of the protection, however, is not known. It may be that the pre-smoked mice have a smaller respiratory minute-volume or that the smoke causes increased secretion of protective bronchial mucus. We have no information on these points. To find out whether smoke acquires any peculiar irritant properties by being in contact with SO_2, a flow of smoky air was divided into two portions. One portion was administered directly to 20 mice, while the other was mixed with SO_2 (5,070 mg. per cubic metre; 1,900 p.p.m.). The SO_2 was then removed from this second portion of air by bubbling through sodium carbonate solution, and the resultant air flow, with its burden of smoke, was administered to a second batch of 20 mice. Prolonged exposure (77 hours; average smoke concentration 50 mg. per cubic metre) caused no fatalities in either group of mice; seven in each batch were kept for three months and they remained in good health. Histological examination of the lungs of all the mice showed no differences between those which had received ordinary smoke and those which had breathed smoke which had been in contact with SO_2.

Sulphuric Acid Mist

Guinea-pigs are much more sensitive to H_2SO_4 mist than any other species; using these, we found that a mist with the larger particles was more toxic than one with smaller particles; and that reducing the temperature of the exposure chamber, but keeping the particle size constant, increased the toxicity of the mist (see Table).

Estimated Median Lethal Concentration (LC_{50}) of H_2SO_4 Mist for Guinea-pigs with an Eight-hour Exposure

Temperature	Particle Mass Median Diameter	LC_{50} (mg. cubic metre)
Room (20° C.) ..	2·7 μ	28·8
Room (20° C.) ..	0·8 μ	60·9
0° C.	0·8 μ	49·0

In high concentrations of mist the guinea-pigs die rapidly with bronchial spasm and a resultant emphysema; in smaller concentrations death is slower and there is more extensive pulmonary damage, including bronchial desquamation, haemorrhagic consolidation, oedema, and emphysema.

Early in the experiments it was noticed that fluctuations in the acid content of the mist occurred, and these were traced to the ammonia evolved from the faecal droppings and urine of the animals, which neutralized the acid. These fluctuations could be prevented by keeping the animals on a wire mesh above a tray of 10% H_2SO_4. Under these conditions reproducible results could be obtained.

The other species examined—monkeys, goats, rabbits, rats, and mice—are much less sensitive to H_2SO_4 mist (Cameron, 1954; Pattle, Burgess, and Cullumbine, 1956); and in one experiment a rabbit survived a concentration of 400 p.p.m. for four days. The guinea-pig is known to be especially susceptible to conditions inducing bronchial spasm, and it is those individuals of the human species with a similar predisposition who are the more severely affected by smog atmospheres.

The variation in susceptibility of different individuals to H_2SO_4 mist is illustrated by our own exposure of human subjects (Van M. Sim and R. E. Pattle, unpublished results, 1955). Mist concentrations of 10 p.p.m., with the M.M.D. of the particles about 1 μ, were found to be highly irritant to the throat, although with prolonged exposure this irritation tended to decrease. If repeated coughing occurred, pain developed in the upper part of the chest. Most of the subjects suffered no long-term effects from an hour's exposure to this mist, but one subject exposed for 30 minutes had "wheezing," coughing, and expectoration for some hours; another subject continued to "wheeze" for two months.

Increasing the particle size of the mist also increased the irritancy, just as it increased the toxicity of the mist to guinea-pigs. Thus a mist of particle size about 1.5 μ M.M.D. was as irritant at 5 p.p.m. as the former mist at 10 p.p.m.

Ammonia was found to annul the irritant properties of H_2SO_4 mist and also those of atmospheres containing SO_2.

Magnesium oxide smoke removed SO_2 from the atmosphere, but even when present in excess did not affect the irritant properties of H_2SO_4 mist.

Smoke

Smoke itself seems to be very inert so far as its acute toxicity is concerned. Our experiments indicate that the smoke from a kerosene lamp has a median lethal dosage to mice of the order of 1,500 mg. per cubic metre for 200 minutes.

Coal-tar Distillates

The effect of these is irregular; in one case dosages of 2,000 mg. per cubic metre of solid and liquid tar for 500 minutes produced no fatalities among exposed mice, but in another experiment with guinea-pigs and mice there were deaths due to irritation of the whole respiratory system.

Wood Distillates

Wood distillates have a much greater content of irritant aldehydes than coal distillates, but the effect of these irritants is masked by the presence of carbon monoxide in the wood gas. When suitably diluted they cause damage to the whole respiratory tract, especially to the trachea and bronchi.

Diesel Fumes

It has been suggested that the fumes from diesel engines may contribute irritant substances to a smog atmosphere. It is known that, because of their lower CO content, these fumes are normally less lethal than those from petrol engines; but Turner (1955) has claimed that diesel engines which are not in good mechanical condition produce more harmful fumes than those without defects. Because of the variety of toxic agents which diesel fumes contain investigation of their toxicity is difficult. Holtz *et al.* (1940) have indicated how the carbon monoxide, nitrogen oxides, and aldehyde contents in diesel fumes vary with changes in the fuel–air ratio.

We have exposed mice, guinea-pigs, and rabbits for varying periods of time to the fumes from a single-cylinder diesel engine (R. E. Pattle, H. Stretch, K. Sinclair, F. Burgess, and J. A. G. Edginton, unpublished results, 1955). Four conditions of engine-running were investigated and concentrations of CO, NO, NO_2, aldehydes, vanadium, and several other substances were determined. The results of these experiments are to be reported in detail elsewhere; the most significant findings under each condition were as follows.

A. *Fuel–Air Ratio 0.0121,* power output low, good injector, air inlet open: No animals died in two experiments in which the exposure was in each case for five hours. In another experiment all the guinea-pigs, half the rabbits, and 20% of the mice were dead after seven hours' exposure. At necropsy all the animals showed gross damage to all parts of the respiratory tract, varying degrees of tracheitis, pulmonary congestion, consolidation, oedema, and emphysema being present. The fumes were highly irritant to the human eye, and the main causes of death were considered to be organic irritants of the acrolein type and NO_2.

B. *Fuel–Air Ratio 0.0193,* power output 5.5 B.H.P., good injector, air inlet open: The fumes were less acrid but more toxic than in A. A five-hour exposure caused 90% of the guinea-pigs, 48% of the mice, but no rabbits to die. Post-mortem examination revealed gross pulmonary oedema, with some patchy areas of consolidation and emphysema. In contrast to the animals dying under condition A, tracheal damage was here slight. The main cause of death was considered to be NO_2.

C. *Fuel–Air Ratio 0.0199,* power output 5.5 B.H.P., worn injector, air inlet open: Here the fumes were much less acrid and less toxic than in B. A five-hour exposure killed 60% of the guinea-pigs but only 1/40 mice, and no rabbits. The post-mortem pulmonary damage was similar to that occurring in B and was considered to be due to NO_2.

D. *Fuel–Air Ratio 0.033,* power output low, good injector, air inlet restricted: The fumes were intensely irritating and more toxic than under conditions A, B, and C. The mice died first, but all the animals were dead before the end of the five-hour exposure. At necropsy the lungs of the mice showed intense congestion and small capillary haemorrhages. The degree of lung damage was greater in the guinea-pigs and rabbits, and these species showed a severe tracheobronchitis. The blood carboxyhaemoglobin content in the mice was about 60% and in the guinea-pigs and rabbits about 50%. The main causes of death were considered to be CO in the mice and in the other two species CO together with irritants.

It should be noted that under none of these conditions was a black smoke produced. White fumes were sometimes present in A, and condition D produced a dense white smoke, apparently consisting mainly of unburnt oil. There were more oxides of nitrogen under moderate load (B) than under light load (A). The aldehyde content was greater under the light load and was very high when the air intake was obstructed (D). In our experiments, therefore, three main toxic agents were recognized: irritant aldehydes, NO_2, and CO. Each was always present in the diesel fumes, but their relative importance varied with the running conditions.

All our diesel fumes contained NO in greater quantities than NO_2; the toxicity and effects of NO are somewhat similar to those of CO. No vanadium was found in the fumes.

Further investigation of the toxicity of diesel fumes under conditions in which the exhaust is smoky is in hand.

The irritancy to man of small concentrations of various aldehyde vapours has been assessed (Van M. Sim and R. E. Pattle, unpublished results, 1955). The unsaturated aldehydes—acrolein and crotonic aldehyde—are highly irritant and cause lacrimation in concentrations of 1 p.p.m. and 4 p.p.m. respectively, while the corresponding saturated compounds—propionic and butyric aldehydes—are almost non-irritant in concentrations of 200 p.p.m. Acetaldehyde, isobutyric aldehyde, and *n*-valeric aldehyde are likewise almost non-irritant. Formaldehyde is intermediate between the two groups, 12 p.p.m. producing severe irritation. Since the individual aldehydes vary so much in their irritant properties, determination of the total aldehyde content of diesel fumes may not provide a good estimate of their irritant potentialities.

Mice, guinea-pigs, and rabbits have been exposed for six hours to a concentration of acrolein of 24.4 mg. per cubic metre (10.5 p.p.m.). This caused the death of about 50% in each species. The post-mortem picture was one of severe tracheobronchitis with pulmonary oedema, consolidation, congestion, and emphysema.

Field Work

We were permitted to take samples at the Dunn Laboratories at St. Bartholomew's Hospital in the fog of January 4–6, 1956. This fog was much less dense than that of 1952. The salient fact found was that filter samples taken up to 4.20 a.m. on January 5 were alkaline (maximum equivalent to 0.16 p.p.m. of ammonia, SO_2 concentration during sampling was 1.16 p.p.m.), whereas samples taken from 9 a.m. on that day until the fog dispersed on January 6 were acid (maximum 0.05 p.p.m., as H_2SO_4). The nature of the alkaline matter present is unknown; alkali carbonates as aerosols would react with SO_2, so it was probably organic. The acid (which may have been present in small quantities while the filter samples were, as a whole, still alkaline) may have been sulphuric. Impaction of droplets on slides coated with indicator (N. W. Wootten, unpublished results, 1956) showed that the acid was present in droplets of 10 μ M.M.D., which were far fewer in number than were the smoke particles.

The fog when inhaled through the mouth produced slight tickling at the back of the throat, similar to that produced by inhaling H_2SO_4 mist in very small concentrations (<0.1 p.p.m.). The irritation was very inconstant, and was not severe enough to cause coughing; it was not possible to determine whether it was alleviated by ammonia. It was not present when a Siebe Gorman "microfilter" was worn. On this occasion, therefore, H_2SO_4 mist was not a major constituent; such respiratory effects as the fog produced (as described above) in otherwise healthy persons could be attributable to gaseous SO_2 alone. The fog had no effect on guinea-pigs exposed to it.

Discussion

Our experiments have indicated that many of the possible contaminants of the atmosphere are highly irritant substances. SO_2, H_2SO_4 mist, certain aldehydes, and NO_2 can all produce death in animals from irritation of the airway and/or pulmonary tissues. CO concentration, particle size, and cold are other variants which might influence toxicity. In general our researches so far suggest that sulphur compounds are important acute toxic agents in smog (Firket, 1937).

The peak concentration of SO_2 in the 1952 London smog was 1.34 p.p.m. (say 3.58 mg. per cubic metre at 20° C.); but this was an average figure for a 48-hour period, so that at times the actual concentration may have been much higher. SO_2 concentrations of this order may in general not be very harmful (Anderson, 1950), but some apparently normal individuals do show an increased airway resistance during exposure. Asthmatics and bronchitics may, of course, react more dramatically.

H_2SO_4 mist is both more irritant to man and more toxic to guinea-pigs, especially with medium-sized particles, which may impact better in the larynx and trachea. It is not certain whether H_2SO_4 was present in the 1952 smog, but Ellis (1931) has found concentrations of it in fogs to be as much as three times that of SO_2. Therefore, an average concentration of 4 p.p.m. might have existed in the London fog of 1952; with a suitable particle size and temperature, such a concentration might produce long-lasting respiratory symptoms in a proportion of otherwise normal men, and those with a pre-existing respiratory ailment might have a more serious response to a smaller concentration.

If H_2SO_4 and SO_2 are important toxic agents in smog their effects could be neutralized by means of ammonia. Indoors this is easy; the amount of ammonia required to neutralize all the sulphur acids in a house or hospital ward would be of the order of 2 g. Ammonia is a comparatively harmless substance; the "threshold limit" for man is given as 100 p.p.m. Ammonia gas could be added to the output of large chimneys to neutralize their SO_2 content.

Nitrous fumes, CO, and irritant aldehydes are emitted into the atmosphere from the exhausts of diesel engines. It is impossible, at present, to say how important these contaminants may be. NO_2 is formed in large quantities by the petrol engine (Hanson and Egerton, 1937); the fumes from this engine contain more CO but less aldehyde than those from a diesel engine. Petrol-engine fumes should therefore, even apart from their CO content, be at least as toxic as diesel fumes, although they would probably have less effect on the trachea and bronchi.

One of the difficulties in interpreting experimental data from so-called normal although sometimes susceptible animals and men in terms of morbidity and mortality in fog is that the latter affects only a specially sensitive small proportion of the general population. A significant observation was made in the SO_2 experiments described above. Here it was noticed that in the early stages, when the mortality was low, small differences in sensitivity (for example, between fresh and pre-smoked mice) gave rise to much larger differences in mortality. This is to be expected if the lethal dosage is distributed according to a "normal" law. If a similar phenomenon appeared in human mortality during smog it would mean that a slight increase in the contamination or duration of the smog would lead to a large increase in mortality; while if the fog contained a number of irritants, elimination of any one of them (for instance, coal distillates by reducing coal burning or sulphur oxides by means of ammonia) would reduce mortality considerably. In such a phenomenon could lie the greater lethality of, for example, the 1952 London smog as compared with others.

Summary

In a study of potential atmospheric pollutants, the effects on animals of sulphuric acid mist, sulphur dioxide, smoke, mixtures of SO_2 and smoke, coal distillates, wood distillates, acrolein, and diesel fumes (under four different running conditions) have been investigated. The guinea-pig is very sensitive to sulphuric acid mist, but, apart from this, the concentrations of pollutants required to produce any effect on animals are very much greater than those found in smogs.

The effects of H_2SO_4 mist, SO_2, and a number of aldehydes on human beings have been studied. Sulphur dioxide in low concentration causes bronchoconstriction in certain cases; sulphuric acid mist can cause bronchitic symptoms, and is irritant in concentrations below 0.1 p.p.m. The toxicity of these compounds is annulled by ammonia.

Some results obtained during the London smog of January 4–6, 1956, are described.

It is concluded that the toxic effects of smog are due to the action of small quantities of pollutants on

exceptionally sensitive human beings; the substances concerned are probably, but not certainly, the sulphur compounds.

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SPLENOPORTAL VENOGRAPHY FOR EVALUATING ABNORMALITIES OF PORTAL CIRCULATION

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Splenoportal venography by percutaneous injection into the splenic pulp was first performed by Boulvin *et al.* in 1951. A large number of splenoportal venograms have been carried out by different observers and much useful information has been gathered from visualization of the portal circulation. The communication by Atkinson *et al.* (1955) is particularly valuable in this respect. We became interested in the procedure after reading the paper by Dreyer and Budtz-Olsen (1952), and since that time a series of 46 successful splenoportal venograms have been performed by the method of percutaneous injection into the splenic pulp.

Most of these cases were subsequently operated upon for splenectomy, or splenorenal shunt, or ligation of hepatic and splenic arteries. Opportunity therefore presented itself for correlating the pre-operative assessment of the splenoportal circulation, as judged by the venographic procedure, with the actual anatomical state of the circulation, the portal venous pressure, and the naked-eye and histological state of the liver.

This communication is based mainly on the findings of the cases subjected to operation, but also includes a few cases which were not operated on but in which the splenoportal venograms were studied and interpreted along with the clinical diagnosis.

Certain suggestive venographic patterns have been formulated as a result of this study.

Clinical Material and Investigation

Of 54 cases in which splenic venography was attempted, successful venograms giving significant information were obtained in 46 (see Table), 5 were unsuccessful owing to spasm of the splenic vein, and in 3 others the findings were inconclusive. Operations were carried out in 32 cases—12 of tropical splenomegaly of uncertain origin, 10 of splenomegalic cirrhosis, 6 of portal cirrhosis, and 4 of infrahepatic obstruction of the splenoportal system. In each of these cases, the portal venous pressure was measured at the time of operation, the naked-eye appearance of the liver noted, and a biopsy taken. When splenectomy was performed the weight of the spleen was recorded and its histology subsequently studied.

Analysis of 46 Cases with Successful Venograms

Nature of Case	Operated	Non-operated	Total
1. Tropical splenomegaly ..	12	0	12
2. Infrahepatic obstruction ..	4	2 (1 confirmed at necropsy)	6
3. Cirrhosis of liver:			
Splenomegalic	10	3	13
Portal	6 } 16	2 } 7	8 } 23
Biliary	0	1	1
Nodular hyperplasia ..	0	1	1
4. Suprahepatic obstruction ..	0	5	5
Total	32	14	46

The series of 14 cases which were not operated on included 3 of splenomegalic cirrhosis, 1 of biliary cirrhosis, 2 of portal cirrhosis, 1 of nodular hyperplasia following subacute hepatic necrosis, and 2 of infrahepatic obstruction of the splenic vein. In one of the cases in this last group obstruction of the splenic vein was confirmed at necropsy. In the remaining 5 cases the clinical features were suggestive of suprahepatic obstruction of the hepatic venous system.

Results

As a result of this study it seems that the venographic appearances fall into four characteristic patterns.

1. Pattern of Tropical Splenomegaly of Uncertain Origin (12 cases, all operated on).—In this type the splenic and portal veins were very dilated and tortuous. In the absence of secondary cirrhotic changes in the liver, collaterals were not present in any case. The bifurcation of the portal vein at the porta hepatis was well seen. The intrahepatic radicals were very faint and the peripheral branches were indistinct. However, in a few cases, when they were faintly visualized, the pattern did not show any distortion (Fig. 1).

2. Pattern of Infrahepatic Obstruction (6 cases: 4 operated; 1 not operated; 1 proved by necropsy).—In splenic vein obstruction the dye terminated abruptly at some part in its course (Fig. 2), whereas in cavernomatous transformation of the portal vein (Fig. 3) the dye became diffusely distributed over numerous small tortuous channels (Das and Basu, 1956). In both cases many collaterals were present.

3. Pattern of Intrahepatic Obstruction due to Cirrhosis of Liver (23 cases; 16 operated; 7 not operated).—This group can be subdivided into two categories.

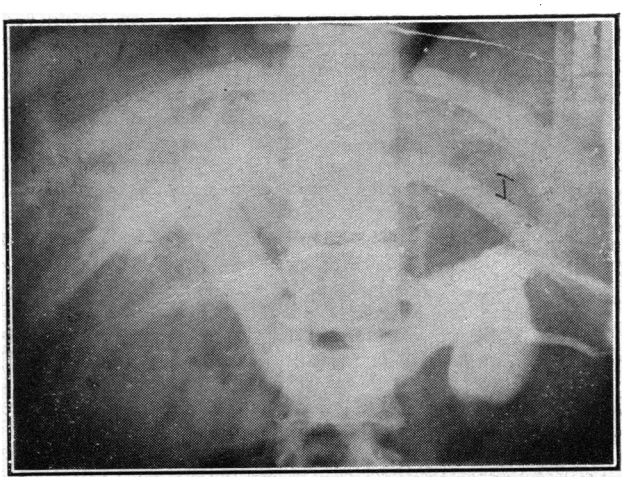

FIG. 1.—Venogram in a case of tropical splenomegaly, showing marked dilatation and tortuosity of the splenic and portal veins. The intrahepatic radicles are poorly seen.