Today's Treatment

Drug-induced diseases

Drug-induced respiratory disease

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It has been common knowledge for many years that some drugs in everyday use may cause or aggravate respiratory disease. Familiar examples are aspirin, which can provoke an acute attack of asthma; opiates and barbiturates, which can precipitate ventilatory failure in chronic bronchitis; and liquid paraffin, which can spill over from the oesophagus into the trachea and produce lipoid pneumonia. Nevertheless, it was not until recently that the concept of drug-induced respiratory disease engaged the attention and interest of the medical profession. Although the bronchi and lungs are less vulnerable to the harmful effects of drugs than the gastrointestinal tract, liver, kidneys, and nervous system, reported instances of drug-induced respiratory disease have steadily increased. This must be due in part to the introduction of new therapeutic agents, but other factors may include a higher index of suspicion that any obscure respiratory illness may be drug-induced and an increasing awareness that the administration of therapeutic agents, such as antibiotics and immunosuppressive drugs, which have no specific action on the lungs, may indirectly be responsible for pulmonary disease, particularly infections.

Drugs can affect the respiratory system by:

- (1) exerting specific pharmacological effects on bronchial calibre or pulmonary function;
- (2) mediating allergic reactions in the bronchi or lungs;
- (3) inducing a syndrome resembling systemic lupus erythematosus with pulmonary and pleural manifestations;
- (4) producing various obscure forms of diffuse pulmonary disease affecting the alveoli or the alveolar walls or both;
- (5) exposing patients to opportunist pulmonary infections with bacteria, viruses, fungi, or protozoa as a consequence of therapeutic immunosuppression or broad-spectrum antibacterial therapy;
- (6) disturbing the normal mechanisms of coagulation and causing either thromboembolic disease or pulmonary haemorrhage; and
- (7) producing focal lesions in the lungs when inhaled accidentally or as a diagnostic or therapeutic measure.

Specific pharmacological effects

Opiates, barbiturates, and even milder sedative drugs, such as nitrazepam or diazepam, cause central depression of respiration

and may be responsible for the onset of ventilatory failure in patients with chronic airflow obstruction (bronchitis and emphysema) and bronchial asthma. Oxygen treatment, by reducing hypoxic respiratory drive in these subjects, may have the same effect if the inspired oxygen concentration is too high.

In a different category are drugs used in treating various non-respiratory disorders, which cause bronchoconstriction either by parasympathetic stimulation (cholinergic drugs) or by beta-adrenoreceptor blockade. The most commonly prescribed drugs in the second category are propranolol and oxprenolol, both of which may provoke severe bronchospasm in patients with asthma. The newer "cardioselective" beta-blocking drugs, such as metoprolol, acebutolol, and atenolol, although less apt to induce bronchoconstriction, may do so in some asthmatic patients, and should be prescribed with equal caution in such individuals.

Allergic reactions

Signs of respiratory allergy, which include bronchial asthma and pulmonary eosinophilia, may result from taking a variety of therapeutic agents. These include proteins with inherent antigenic potential, such as antisera and vaccines, and certain drugs of low molecular weight acting as haptens (substances that acquire antigenic properties when chemically bound to a protein). In sensitised individuals all these therapeutic agents can produce or aggravate allergic respiratory disease, but it is not clear why some of them cause asthma alone and others only eosinophilic pulmonary infiltrations, while some patients develop both bronchial and pulmonary reactions.

There is some doubt whether asthma provoked by aspirin represents a true hypersensitivity response, but recent evidence that aspirin-induced bronchoconstriction is inhibited by sodium cromoglycate inhalation favours that hypothesis. A similar doubt, still unresolved, exists in relation to the nature of bronchial reactions to contrast media containing iodides. The drugs reported to cause the various forms of allergic respiratory disorder are listed in table I.

Pulmonary and pleural manifestations of a drug-induced syndrome resembling systemic lupus erythematosus

Some drugs, including hydralazine, procainamide, practolol, isoniazid, and phenytoin, are known to give rise to a syndrome closely resembling systemic lupus erythematosus, both clinically and serologically. These patients often develop diffuse pulmonary lesions and pleural thickening.

Patients usually recover when the drug is withdrawn, but the observation that in some instances the condition persists, and even progresses, raises the question as to whether the action of these drugs is merely to uncover latent forms of the disease.

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TABLE I—*Drugs reported to cause allergic respiratory disorders*

Bronchial asthma	Penicillin and other antibiotics Antisera and vaccines Allergenic extracts used for hyposensitisation Aspirin Monoamine-oxidase inhibitors Iodine-containing contrast media Iron dextran
Bronchorrhoea	Iodides
Pulmonary eosinophilia	Nitrofurantoin Para-aminosalicylic acid Sulphasalazine Other sulphonamides Imipramine Chlorpropamide Phenylbutazone Aspirin Penicillin and other antibiotics
Allergic alveolitis	Pituitary snuff

Other types of diffuse pulmonary disease

Drug-induced lung disease in this category is not associated with identifiable immune responses, and it has been postulated that they may be related to some form of enzymatic abnormality. They form a heterogeneous histopathological group, ranging from the desquamative alveolitis and interstitial fibrosis caused by the cytotoxic drugs busulphan and bleomycin to a syndrome resembling adult hyaline membrane disease ("fibrinous pneumonia"), which has been observed after treatment with the now obsolete antihypertensive drug methonium and some related compounds, and to overdosage of the tricyclic antidepressant amitriptyline.

The pathological changes in the second group bear some resemblance to those seen in pulmonary oxygen toxicity (itself to be regarded as a form of drug-induced lung disease) and paraquat poisoning. It is conceivable that these conditions may all be related to inhibition of surfactant production in the pulmonary alveoli.

Opportunist pulmonary infections

With the increasing use of cytotoxic drugs in malignant disease, immunosuppressive drugs in transplantation surgery and in the treatment of diseases such as bronchial asthma and autoimmune disorders, and of broad-spectrum antibiotic treatment, many patients are now being exposed to the risk of developing opportunist pulmonary infection (table II). Although

TABLE II—*Examples of drug-induced opportunist pulmonary infections*

Bacterial	<i>Staphylococcus pyogenes</i> Gram-negative bacilli <i>Mycobacterium tuberculosis</i>
Viral	Cytomegalovirus
Fungal	<i>Aspergillus fumigatus</i> <i>Candida albicans</i> <i>Cryptococcus neoformans</i>
Protozoal	<i>Pneumocystis carinii</i>

these infections might not be regarded as specific forms of drug-induced lung disease, they are numerically important, and probably account for more fatalities than all the other drugs discussed in this article.

It is clearly essential to make a positive microbiological diagnosis in these cases at the earliest possible stage, so that treatment can be started without delay. The technique of transbronchial lung biopsy may be required in cases of suspected *Pneumocystis carinii* pneumonia.

Coagulation disorders causing pulmonary thromboembolism or pulmonary haemorrhage

Oestrogen-containing oral contraceptives predispose to pulmonary thromboembolism, but even with the aid of modern investigative procedures it is often extremely difficult to determine whether or not an episode of pleural pain is due to pulmonary infarction, and to decide if the contraceptive pill should be withdrawn. Cytotoxic drugs may cause haemoptysis by reducing the platelet count.

Focal pulmonary lesions caused by inhalation

Nasal drops or sprays consisting of vasoconstrictive drugs suspended in liquid paraffin were once a not uncommon cause of lipid granulomas in the lungs, but those forms of treatment have now been abandoned. This type of lesion is, however, still seen occasionally in patients who consume large amounts of liquid paraffin for constipation, because small quantities of this mineral oil may ooze into the trachea during swallowing.

Much larger quantities may enter the air passages in patients with cardiospasm, who often have an incompetent cricopharyngeal sphincter, and such patients may develop extensive lipid pneumonia. Iodine-containing opaque media suspended in arachis oil, used for bronchographic examination, may also produce lipid granulomas.

Conclusion

There are two main reasons why doctors are often slow to recognise drug-induced respiratory disease. The first is failure to elicit detailed information about patients' current or recent drug treatment. The second is ignorance of the identity of those therapeutic agents that are capable of producing bronchial and pulmonary disease. It may also be the case that recently introduced drugs, not mentioned in this article, may prove to have adverse effects, so far unrecognised, on the respiratory system, and the vital importance of reporting every suspected case of drug-induced disease to the Committee on Safety of Medicines cannot be over-emphasised.

A man of 74, physically active all his life, is in good health but at a routine examination was found to have a BP of 210/140, confirmed by subsequent readings. Is any treatment advisable?

Blood pressures of 210/140 in younger patients need urgent treatment for there is some risk of evolution into a malignant phase. In later life there is still no published evidence to prove that hypotensive treatment is of value, but one or two trials are in progress which suggest that it may be. It is a central problem of hypertension that the most valuable treatment is given to the asymptomatic patient, and in this case I would encourage the subject to seek treatment to control his blood pressure. This will mean medication but need not prevent all exercise, which remains valuable at any stage in life.

Why do onions and Jerusalem artichokes produce above-normal amounts of flatus?

Excess flatus is usually caused by foods containing carbohydrates that are not digested and absorbed by the human gut, but which can be fermented by colonic bacteria. Most research has been done on baked beans, in which stachyose and raffinose seem to be the substrates chiefly responsible for flatus production. Although artichokes and onions contain less than half the total amount of carbohydrate (per 100 g) found in beans, presumably they, also, have undigestible oligosaccharides, but information on this is not available in authoritative food tables.