attacks elastin.[3] Emphysema can also be produced in dogs by aerosol homogenates of human leucocytes,[4] which are thought to be the main source of enzymes damaging the lung in patients with α_1-antitrypsin deficiency—indeed, α_1-antitrypsin is a potent inhibitor of elastase derived from human granulocytes.[5] Further, α_1-antitrypsin also inhibits pancreatic elastase,[6] and a correlation at necropsy between the amount of this enzyme in the pancreas and the incidence of emphysema has been recorded.[7] A possible relationship between pancreatic enzymes and emphysema was also suggested by a report of a patient who developed concurrently an acute relapsing pancreatitis and a rapidly progressive basal emphysema.[8]

If, as this evidence suggests, proteolytic enzymes can cause emphysema, the disease should be abnormally frequent among people who are short of enzyme inhibitors. This is certainly true of those with a severe inherited deficiency of α_1-antitrypsin (the homozygotes). While it is not universally agreed that heterozygotes are more prone to emphysema,[9] recent work has shown that both the deterioration in lung function among cigarette smokers[10] and coal workers,[11] and the loss of elastic lung recoil which occurs with increasing age,[12] proceed more rapidly in heterozygotes than in the normal population. It has also been claimed that heterozygotes with chronic obstructive pulmonary disease have an abnormal pattern of regional lung function distinct from that in patients with normal α_1-antitrypsin levels[13]—but this apparent difference could equally well have resulted from the methods used for selection of the two groups of patients. Further epidemiological studies may well solve the problem of heterozygotes, but the answer may be of more interest to geneticists than to the clinician seeking remediable causes for emphysema.

The message of the α_1-antitrypsin story for clinicians is that proteolytic enzymes might actually cause the disease. The factors leading to an excess of such enzymes in the lung—and these may in theory include anything which provokes a cellular infiltrate—could be as relevant to the pathogenesis of emphysema as a deficiency of enzyme inhibitors. Indeed, the serum trypsin inhibitory capacity (T.I.C.) can actually be raised in emphysema, not only in patients with purulent sputum[14] but also in those with no evidence of infection;[8 15] and this increase might in some cases be a specific response to the release of proteolytic enzymes into the blood stream. It is evident that measurement of the serum T.I.C., for which simple screening tests are now available,[16] is an important investigation in every case of emphysema; but perhaps more attention should be paid to raised as well as to reduced levels of T.I.C. and also to the perfection of simple techniques for the assay of proteolytic enzymes themselves.

The emphysema associated with α_1-antitrypsin deficiency is panlobular and mainly basal in site. This basal distribution has been attributed to the fact that in the upright posture basal perfusion exceeds that of the apex and that the proteolytic enzyme presumed to be the causative agent is blood-borne. A corollary to this is that known air-borne factors predisposing to emphysema, including cigarette smoke,[17] cadmium fumes,[18] and coal dust,[19] tend to induce a proximal or centrilobular lesion which, unlike panlobular emphysema, favours the apices of the lungs.[20 21] It seems reasonable that an air-borne pathogen should have its greatest impact on the more proximal alveoli[22] while the apical predominance may relate to the lung apex being subject to greater inflationary stresses and having a higher ratio of ventilation to perfusion than the base.[23] Certainly other air-borne diseases such as tuberculosis, silicosis, and some forms of extrinsic allergic alveolitis also favour the apices; but there are mechanisms whereby air-borne agents can mainly injure the bases. Those which cause bronchitis, for example, may damage dependent parts[24] through retention of mucus secretions, while inhaled pollutants such as sulphur dioxide and ozone[25] may be absorbed in the upper respiratory passages and then excreted through the lower zones of the lung, where the blood flow is greatest.

Much is still to be discovered about the causes of emphysema; but the precise role of tissue enzymes and air pollution and the pathogenetic significance of zonal distribution, both within the lobule and in the lung as a whole, surely deserve further exploration.

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Animal Experiments

About a century ago the British Association for the Advancement of Science and the B.M.A. both expressed views about the possibility of unjustifiable suffering being inflicted on animals in the name of science, as also did a number of scientists, among them Charles Darwin and T. H. Huxley, and some lay people. This led to the appointment of a Royal Commission[1] in 1875 and the Cruelty to Animals Act[2] of 1876.

The 1876 Act is still in operation today, but would have been hopelessly overtaken by events were it not that those who use animals in Britain have always shown sufficient concern for their welfare to make an apparently obsolete Act work in practice very well. In fact British scientists have a good record, which was confirmed by successive reports[1 3] of the Royal Commission and by the Littlewood Committee[4] appointed in 1963. Nevertheless there have never been lacking those who disapprove of animal experiments on principle and who will sometimes employ any argument, rational or otherwise, to attack those who need to use animals in their work.

The case for using animals in the pursuit of scientific and medical objectives may be regarded as chiefly utilitarian, and in the light of experience this is overwhelming. But it should not be allowed to dull our ethical sensibilities. We all collectively have a responsibility for the proper treatment of the animals that serve us so well, and even antivivisectionists cannot avoid benefiting from the knowledge thus discovered. Is it possible to measure the price that is paid by the animals for the advantages we gain from them, and is it possible to cast a sort of ethical balance sheet?

Some experiments look gory and distasteful to the unaccustomed eye, and such feelings are not necessarily dispelled by the knowledge that the animal is irrecoverably unconscious and therefore there can be no question of suffering. Other experiments involving perhaps a small dietary change or a simple inoculation or even a manipulation of the environment may yet lead to dire consequences for the animal. If we are concerned with humanitarianism, are we more concerned with what looks bad or what, from the animals' point of view, is bad? If we choose the latter we must assume or acquire some understanding of the animal before we can say with any competence whether it is suffering and, if so, in what degree.

So we come to the practical considerations. To try to abolish animal experimentation must be regarded as a hopeless cause and would in fact bring in its train much more suffering than it could ever save. To try to reduce the volume of animal experimentation or its severity is quite another matter which should surely be an obligation placed squarely on the shoulders of those who use animals. There are many voices raised today suggesting that too many animals are used for purposes for which alternative methods are or could be made available; that some of the reasons for doing animal experimentation are trivial or venal; that too much secrecy surrounds the use of animals in the laboratory; and that the judgement is too much left in the hands of those using the animals who must therefore be presumed to have a vested interest in such use.

The replacement of all animal experiments by non-sentient systems is an ideal totally unattainable, because as Professor J. L. Gowans explains on p. 557 animal experiments, even a very large number of them, will always be needed to find out whether the non-sentient system is in fact an adequate substitute for the whole animal. The allegation that some animal experiments are trivially motivated has prima facie validity; for example, it might be thought that with so many people killing themselves with cigarette smoking it is not really necessary to subject monkeys and other animals to tobacco smoke, whatever interest this may have for the tobacco industry. The testing of cosmetics for safety has come under frequent attack, but while women and men insist on using cosmetics they surely must demand that they are safe to use. So called "natural" or well-established substances are not necessarily safe; ragwort tea, which can contain a liver carcinogen, is still found in some health stores, and even aspirin is not totally devoid of risk.

As for the other criticisms, animal experiments, like most other experiments, cannot be opened to the public any more than countless other professional operations. But it is not secrecy, still less secretiveness, that is the reason for refusing admission to laboratories and animal houses of any member of the public who thinks he has the right to go in. Every hotel has some doors marked private, and so indeed has almost every other place to which the public have partial access; they could not be operated otherwise.

Finally, is it right that in considering the justifiability of a given experiment the experimenter shall be judge in his own case? Nearly always he will in fact be by far the best informed person, but can we guarantee that he is capable of overcoming his understandable bias? The answer is that we can, because the situation incorporates two vital safeguards. The first is the opinion of the experimenter's own colleagues. Scientists are never slow to criticize one another, and if occasion ever arose they might be more willing to criticize questionable experiments more openly were it not for their fear that their criticisms would be taken up too enthusiastically by antivivisectionists and used, not as a corrective in detail, but as a condemnation in general. It is this fear which is itself the greatest condemnation of the antivivisectionist movement. The second safeguard is the Home Office inspectorate, and this was well recognized by the Littlewood Committee, which recommended an increased number of inspectors in the country. Inspectors visit every laboratory at sufficiently frequent intervals to inform themselves of what goes on there and who is using animals. It would be no more possible to inspect every experiment throughout its total duration than it would be to inspect the luggage of every person coming into the country. But there the analogy ends; those who want to smuggle will never feel that in trying to get away with it they are putting their fellow travellers at risk, whereas the scientist who tried to pull the wool over the inspector's eyes would not only get into trouble himself but would cast a poor reflection on his colleagues.

There is a need for a code of conduct in the use of animals, and it is appropriate that after the lapse of a century those who are most immediately concerned with animal experiments should turn their attention to codifying their ideas and principles. The initiative should come from the scientists, just as the initiative in working out an ethical code for human experiments came from the medical profession. It is not a question of putting one's house in order, because there is no evidence that our house indeed lacks order. But we should make sure that we keep it in order by anticipating the possibility of abuse and taking steps to aviod it.

[1] Royal Commission on the Practice of Subjecting Live Animals to Experiments for Scientific Purposes 1875, *Report*, London, H.M.S.O., 1876.
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Innocent Praecordial Murmurs in Children

Most of the children examined by cardiologists at infant clinics and school surveys have been found to have auscultatory "abnormalities." M. Lesshof and W. Brigden,[1] for example, found murmurs in 96% of healthy children between 3 and 14 years of age. This figure contrasts sharply with a probable prevalence of about 0·5% of actual heart disease in the same age group. Though only the louder of these murmurs may be heard by less skilled auscultators, most children have such frequent medical examinations nowadays that many are discovered—so many that the term "normal heart murmur" is often used when reassuring parents that most of them have no clinical significance.

Murmurs are usually detected in three circumstances: during routine screening at infant clinics, school medical