Papers and Originals

Use and Abuse of Drugs*

Sir DERRICK DUNLOP, B.A., M.D., F.R.C.P., F.R.C.P.ED.

Brit. med. J., 1965, 2, 437-441

It is right and proper that from time to time we should remember and praise the name of Sir Charles Hastings. To be invited to act as the channel along which our praise of him should flow is an honour of which I am deeply sensible. Nevertheless, when I think of the immense erudition and distinction of most of my predecessors in this lectureship my pride at joining their company is tinged with the natural diffidence and alarm which might be felt by a yokel introduced for the first time to polite society, very conscious of the straw sticking out of his ears and the dung all over his boots. Charles Hastings founded the Provincial Medical and Surgical Association, from which the British Medical Association developed, and through it was in a large measure responsible for the Medical Act of 1858, which did so much for the status of our profession and for the protection of the public against impostors. He not only excelled, like most Edinburgh graduates, in the practice of his profession, and in addition was tall, amiable, and prepossessing (I was sorry when his likeness disappeared from the cover of the *British Medical Journal*), but he realized before his time that medicine had assumed a position in our society which demanded that educated people should know something of its scope, responsibilities, trends, and accomplishments; and that it was essential to dispel the illusion, fostered by many gold-headed-cane physicians in his day and by some even now, that it was an esoteric mystery. He would therefore have applauded the fact that his memorial lecture should be specifically intended to interest the lay public in some medical matter of general concern, however much he might have looked askance at the lecturer to-night.

When I qualified in the early 1920s the aspect which medicine presented to the public did not differ very greatly from that depicted in Frith's famous sentimental Victorian picture, "The Doctor." There he was, you remember, with his great brown beard brooding over the sick child in the cottar's house with the inevitable bottle of medicine beside him. Such bottles were largely placebos, to use a word now fashionable to denote inert substances which please, as the patient believes them to contribute active therapy. Doubtless the doctor in the picture, like all good doctors, was to some extent a placebo himself—that is, he deployed his personality as an instrument of therapy. Don't imagine I denigrate him or his simple remedies: to begin with, we now know that placebo medicines are 35% effective in relieving pain; then there was the comforting effect of a leisurely home visit by a kindly educated gentleman (a taboo word nowadays except over public conveniences) with some knowledge of science, medicine, surgery, and midwifery. Perhaps we as teachers of the modern generation have not been guiltless in overemphasizing scientific advances at the expense of patient care. At his best Frith's Victorian doctor did more good and certainly less harm than the worst of the moderns who would immediately have prescribed a bottle of sulpha tablets for the sick child, then tried some injections of penicillin, and,

if that was unavailing, would have telephoned the pharmacist to send round some tetracycline pills. Then, with the situation hopelessly confused, he would not have the faintest idea whether the continuing fever was due to persistence of the disease or to the effect of his medicaments.

The Therapeutic Explosion and its Benefits

Like other egotists I am able to think of the modern medical era as being only that with which I myself have been concerned. Insulin was introduced just before I qualified, and a few years afterwards liver extract, the active principle of which was discovered twenty years later. The advent of the sulphonamides in the 1930s heralded the therapeutic explosion. Since then the mortality from gastro-intestinal infections, the chief cause of infantile deaths, has fallen by over 80% and that from pulmonary infections by nearly 70%, while the mortality from tuberculosis, meningococcal infections, mastoiditis, and venereal disease all show similar or greater declines; diphtheria, from which as late as 1940 there were 2,500 fatal cases in England and Wales alone, has disappeared; typhoid, typhus, tetanus, cholera, plague, yellow fever, rabies, smallpox, measles, whooping-cough, and poliomyelitis can be prevented; many tropical diseases such as malaria have been controlled; and the lives of patients suffering from diabetes and pernicious anaemia can be preserved and considerable relief given to sufferers from hypertension, arthritis, asthma, and many nervous and mental disorders. The list is far from comprehensive and makes inadequate mention of the relief from suffering which the purely symptomatic use of modern drugs confers. Doubtless the all-round improvement in social conditions has contributed to these remarkable results, which since 1930 have added ten years to our average expectation of life; but in this country the use of modern drugs, including bacteriological products, has been a more potent factor.

As the result of all this the pattern of disease which we see nowadays has changed out of recognition. Most hospitals for tuberculosis and many wards in those for infectious diseases have been given over to the care of bronchitics or of old people; children's hospitals, since the conquest of many infections, are largely filled with patients suffering from congenital and metabolic disorders or with surgical emergencies; young people nowadays seldom die from disease, the chief cause of death among them being accident, the second suicide, and the third, a long way behind, the comparatively rare blood disease acute leukaemia; the atmosphere and the length of stay in our mental hospitals have changed out of recognition owing to the use of modern psychotropic drugs; and our general hospitals are mostly filled with patients suffering from the natural processes of ageing—atherosclerotic, cardiac, and cerebrovascular disease—or from cancer, some of which can be prevented by giving up cigarettes, or detected and cured at a very early stage, especially cervical uterine cancer.

* The Sir Charles Hastings Memorial Lecture given at the National Museum of Wales, Cardiff, on 25 March 1965.

The vast saving in mortality resulting from the use of modern drugs is well documented, but the tremendous saving to the national economy which they have effected in diminished morbidity—less time lost from work and fewer and shorter admissions to hospital—is more difficult to compute: taking tuberculosis as an example, it has been estimated with fair accuracy that the saving to this country from the use of anti-tuberculous drugs is about £55m. a year, or about half the total drug bill for the National Health Service.

Cost of Drugs

These great benefits have been achieved only at a price. The cost of drugs, though it has remained steadily as a tenth of the cost of the National Health Service, has progressively risen from £35m. in 1949 to well over £100m. a year now. This has not been due to the overall increase in the price of drugs, as the pharmaceutical price index has remained remarkably steady in comparison with the cost of other commodities, but to the increasing population, to the greater number of prescriptions written, and to the greater use of expensive drugs such as antibiotics, which account for one-quarter of the total drug bill. We must remember to keep in perspective the cost of drugs which have conferred such immense benefits, and to recall that if the annual expenditure on them is over £100m., that on all forms of gambling, on alcoholic drinks, and on tobacco is over £1,000m. for each, none of which is particularly good for us.

Overprescribing

Satirists and enemies of the Health Service have recently depicted the British people as a nation of pill-swallowers. Actually we spend less on medicines per head of the population than any other nation in the Western world with the possible exception of the Danes. Excess elsewhere does not, of course, justify it here, and we must confess that there is a great deal of overprescribing in this country for which there are a number of causes. There are the insistent demands of the public, whose insatiable desire to take medicine is, as Osler said, the chief thing which differentiates man from the lower animals.

Secondly, there are insufficient doctors for the growing population: it is time-consuming to take a careful clinical history, to carry out a thorough examination, and to give wise advice, but it takes only a moment to write a prescription for a symptomatic remedy, and this often satisfies the patient even though we know perfectly well that the prescription of an alkaline mixture does not liquidate a doctor's responsibilities in a case of peptic ulcer, nor does a phenobarbitone tablet do much to heal a broken heart. Faced with fantastically overcrowded surgeries in practice or out-patient clinics in hospital we have all sometimes overprescribed in order to get luncheon, and the habit grows. Unless this country and its Government determine that they want good doctoring, and realize that this is going to be expensive, overprescribing will continue.

Thirdly, there is the formidable and skilled promotion of drugs by the pharmaceutical houses, some of which is subject to justifiable criticism in violating truth and good taste. Nevertheless, the cure for this is in the hands of the medical profession, for no ethical drug (that is, no drug which has to be prescribed and cannot be bought over the counter) can reach the public save through its intermediary. There is no parallel to this situation with any other commodity, in which the industry supplies, the doctor orders, the patient consumes, and the Government pays. Thus the advertising of ethical drugs, on which vast sums of money are expended, is not directed, like the advertising of most commodities, at the population of the country as a whole but at the relatively small number of its duly qualified medical men who are sought after, chased, wooed, and importuned to a fantastic extent. Our outrage at this, as Garai (1964) has suggested, is largely due to our realization that our high opinion of ourselves is evidently not shared by

the drug advertiser. We should stop bemoaning this attack on our professional maturity and begin to realize how justified it must be, for no advertising which does not work will continue to run. In our society the market-place may not be responsive to idealism but it is always sensitive to sales curves. Let the sales of any product decline sharply and remain down and that product will die. Let us as doctors but withhold our approval of new drugs and preparations until conclusive evidence has been presented in support of the claims made for them and it will cease to be economically feasible to market new drugs without such evidence. Ours is the sole and absolute power to determine drug sales, and if we express our wishes on prescription pads our wishes will be heeded, and heeded quickly.

The Pharmaceutical Industry

Though the physician is still finally responsible for the drugs he prescribes he has not for a long time himself culled herbs by the light of the moon and prepared medicines from them. He soon delegated this duty to the pharmacist. In more recent years the great increase in the use of synthetic drugs and the corresponding decrease in that of naturally occurring galenicals have seen a further inevitable delegation, tinged with nostalgic regret, from the pharmacist to the pharmaceutical manufacturer.

Operating under the profit system, the pharmaceutical industry has made enormous contributions to our society. Indeed, nearly all the valuable new drugs of the last 30 years—penicillin and streptomycin are notable exceptions—have been discovered in the manufacturers' laboratories. Nevertheless, the industry has recently been under constant attack, mainly on the grounds that its profits are too great and its drugs excessively expensive, for their selling price may be as much as ten times the cost of their production. The industry replies that it needs large profits on the drugs it actually markets, as research, which so often leads to nothing, is enormously expensive and risky. Further, the industry claims that it must have the full protection of patent rights, for without this the rewards of its capital expenditure and immense technical labour can be stolen by those who have not laboured in the vineyard. The whole matter recently came up acutely in the legal battle over whether the Minister of Health was at liberty to buy for the hospitals inexpensive non-patented drugs from Poland and Italy. Our most eminent legal brains did not apparently find the answer a simple one, though it was finally decided in favour of the Minister by the votes of three judges to two in the House of Lords; but where such luminous minds differ who are we to dogmatize?

At any rate the pharmaceutical industry now contributes over £60m. a year to our export trade, and it is probable that without the mass-marketing techniques which are often so bitterly assailed few of the drugs on which modern medical practice depends would be affordable at all. In some future Utopia it may be that non-commercial motivations will yield the same results without side-effects. Till then we shall have to take the world as we find it and remember that since the October Revolution the state-owned industry in the U.S.S.R. has not produced a single new drug of therapeutic importance. We must therefore be careful not to kill the goose which has laid so many golden therapeutic eggs by excessive bureaucratic restrictions—still less by nationalization.

Toxic Effect of Drugs

We have profited so greatly from modern drugs that their cost in money, though considerable, would probably not be grudged were there not another price to pay. Just as the old horse and buggy, though slow, caused few serious accidents whereas the modern automobile, though very fast, is often a lethal agent, so the old bottle of medicine, though rather ineffective, was usually innocuous, whereas the modern drug is,

like atomic energy, powerful for evil as well as for good. It has been estimated that from 10 to 15% of patients in our general hospitals are suffering to a greater or less extent from our efforts to treat them—from iatrogenic diseases as they are called, or, more optimistically, from diseases due to medical progress. Our powers over nature in applied pharmacology have extended so far that nature seems to have become retaliatory and is exacting a massive retribution. Thus an antibiotic is discovered which sweeps and garnishes the bacterial population from a patient, leaving an organismal vacuum, and, as Nature abhors a vacuum, she peoples it with virulent staphylococci resistant to the antibiotic, so that the last state of that patient is worse than the first; and then man strikes back again with a new antibiotic which the staphylococcus has never met before, and so on it goes. Or, owing to the elimination of malaria by antimalarial drugs, the balance of nature is upset so that overpopulation occurs and the race faces starvation; and then man comes back with contraceptive pills to redress the balance, and what Nature will say to them we do not yet know for certain.

Safety of Drugs Committee

Though we had been well aware for many years of the toxic nature of many of the therapeutic agents we were using, we had been somewhat ostrich-like regarding them: it took the emotional reaction to the thalidomide tragedy to galvanize us out of our somewhat *laissez faire* attitude. Following it, public and medical opinion demanded that an organization independent of the manufacturers be set up for the assessment of the safety of a drug in relation to the purpose for which it was to be used. The resulting Safety of Drugs Committee has now been functioning for a year and a half. It does not itself carry out pharmacological tests or clinical trials of drugs; it simply weighs the manufacturers' submissions on their tests and lays down standards for them. There are three stages in the evaluation of a new drug with each of which the Committee is concerned.

Toxicity Tests

Firstly, toxicity tests are conducted in the laboratory to ensure that a therapeutically promising drug is reasonably safe for clinical trial, to ascertain its best formulation and dosage, and to determine its mode of action and metabolism in animals. A complicated series of tests have been evolved, starting with *in vitro* tests in the laboratory, then pharmacological tests on isolated tissues, and, finally, tests on various species of animals. The difficulty is that there are great differences between species of animals in their reactions to drugs. Man is a distinct species, and it is not always true that a drug which appears safe to animals will be safe for man, or, conversely, that a drug which shows alarming toxicity in animals will necessarily represent the same hazard for man. Though it is manifestly essential for animal tests to precede those on human beings, we must realize that as the result of the requirements which are now insisted upon some effective and safe drugs may never see the light of day, and if we take a retrospective view some useful drugs would never in the present atmosphere have reached clinical trial. Quinine, for example, would probably have been discarded, as it would doubtless have been tested on dogs, who are exquisitely sensitive to it.

The thalidomide disaster inspired the demand for all new drugs to be tested in animals for their effect on the foetus—the so-called teratogenic effect. Nevertheless, it is as well to be quite clear that no test has yet been devised in animals which can with certainty predict that a new drug will or will not have this effect in humans. Admittedly, if a drug is shown to be teratogenic in an animal he would be a bold manufacturer who would market such a drug, but the absence of teratogenicity in animal-testing is no guarantee of its harmlessness to the human

embryo. As Smithells (1965) has emphasized, care by the doctor in the administration of drugs to pregnant women is so far a much more valuable safeguard than tests for teratogenicity. The period of new organ formation in the embryo lasts for about eight weeks from the time of the first missed menstrual period. During this time many adverse factors may have a deleterious effect on the undifferentiated rapidly multiplying cells of the foetus, which, like cancer cells, are extremely susceptible to antimitotic drugs, though these are not commonly used in pregnancy. Certain chemotherapeutic substances such as sulphonamides and antibiotics, designed to interfere with the multiplication of bacterial cells, have also fallen under suspicion, but there is as yet no conclusive proof that they are teratogens. Apart from antimitotic drugs and some hormones, thalidomide remains the only drug proved to be teratogenic in humans. Nevertheless, a responsibility lies on every doctor ordering the administration of any drug to a woman during the first twelve weeks of her pregnancy. On the other hand, the integrity of the embryo is best served by safeguarding the health of the mother, and it would be quite wrong to withhold a drug of known benefit in a serious maternal illness because of the faint theoretical risk of teratogenicity.

Clinical Trials

While, therefore, studies of the efficacy and safety of drugs in animals are valuable, only carefully conducted clinical trials can ultimately resolve the issues of their safety and effectiveness in humans. The second stage in the testing of a new drug thus consists of clinical trials.

Sir Austin Bradford Hill (1960) has reminded us that human experimentation is not just a modern activity. Ringing the changes in treatment from the fillet of a fenny snake to the eye of a newt or the toe of a frog and observing the result was a human experiment. A question was asked of nature by means of a trial on a human being or a series of human beings and impressions followed. They were haphazard impressions, greatly influenced by traditional dogma, and it took aeons of time before, say, blood-letting for fevers was found to be worthless. This is to be contrasted with the extraordinary rapidity with which well-planned controlled trials proved the efficacy of anti-tuberculous drugs and showed how they should be administered in combination. It has indeed been only in the last 30 years that medical science has conducted clinical trials of drugs within a conceptual framework constantly tested by accurate observation and rigorous analysis; in which plans are made to eliminate bias in allocation and bias in evaluation, and the collected data are ultimately subjected to statistical analysis. Such controlled experiments, in which variables are purposely manipulated in a systematic manner for the purpose of delineating correlations with precision and for investigating cause-and-effect relationships, are producing therapeutic benefits to mankind at an ever-increasing rate.

Nevertheless, there is a widespread feeling that what I might call the mediaeval clinical impression type of trial, to which I have adverted and which persisted till 30 years ago, is in some way ethically superior to the modern clinical trial. There is a general tendency to accept the uncontrolled experimentation with unproved drugs to which unsuspecting patients have always been subjected in practice; but if a consultant—still worse a full-time medical professor, who is usually regarded as being totally defective in clinical judgment, common sense, or compassion—carries out a carefully planned clinical trial in hospital, that is regarded as treating National Health Service patients like guinea-pigs and questions may be asked in the House about it. There must always be some patient or a group of patients who receive a new drug for the first time: it is surely desirable that this should happen to them under careful observation by experts in hospital and that the experience of such patients should be made of value to others.

Those doctors who were initially so fortunate as to have been testing insulin, liver extract, the sulphonamides, or penicillin had a relatively easy task: the value of those drugs was immediately apparent without carefully designed trials. More often, however, the problem confronting the investigator is to discover whether a new drug reduces a mortality rate from, say, 10 to 5%. Without an extensive and carefully planned trial this is impossible, and even with such a trial it may be very difficult.

Clinical trials of drugs often involve questions of medical ethics, and the whole problem has been admirably discussed by Witts (1960). I believe that a code of ethics and humanity has through the ages been built into the medical profession, and that clinical trials in this country have been conducted with a very high degree of prudence and caution. There is, however, apt to be a slight difference in attitude between the physician-friend and the physician-experimenter. The former has a personal relationship with his patient, sharing his distress and anxious to alleviate it. Objective experimentation to confirm or refute some therapeutic generalization is apt to be a little foreign to this relationship.

It is therefore not surprising that various authorities have attempted to draft codes of ethics to govern human experimentation. While it is possible to enunciate some very broad and rather platitudinous principles which are really a part and parcel of the doctor's training, it is doubtful whether precise rules can be framed applicable to all the immensely varying circumstances of clinical trials, about which it is so easy to generalize and so difficult to particularize. A rigid ethical ideal may be too restrictive when facing real life problems. The ultimate judge of what is justifiable is not a rigid code of ethics but the conscience of the doctor, which should be a tender one, and the consciences of his colleagues, with whom he should invariably consult about the propriety of his investigations. The end does not always justify the means, and the good things a man does can be made complete only by the things he refuses to do.

Monitoring of Adverse Reactions

Any clinical trial of a drug will of course provide for the record of its short-term toxic effects. Nevertheless, such an effect, occurring perhaps sufficiently often to be of great importance from the point of view of the drug's safety, may yet happen too seldom for it to be encountered during the trial. Thus a serious reaction occurring, say, in 0.1% of cases, possibly constituting a grave drawback to the drug, might never occur during even an extensive clinical trial in hospital. No matter therefore how careful the preparatory work of the pharmacologist and clinician may be, there is ultimately no substitute for years of the routine practical experience of the drug's use in thousands of patients. The third part of the committee's work is thus very important in monitoring all the relevant reports of the adverse effects of drugs after they have been marketed. The extent to which the drug is prescribed is also ascertained, for without this as a denominator the numerator (the number of its toxic reaction) is virtually meaningless.

It is in this sphere that the medical profession can supply an essential service by reporting promptly, as they have been asked to do, any illnesses in their patients which might be the result of drug treatment, and in replying to any inquiries about the health of patients who are receiving or who have received drugs that have fallen under suspicion. Only with such organized accumulation of information in this country and abroad can early warning be given to doctors when it is found that the frequency of reactions to any drug is so great as to constitute a serious hazard.

The thalidomide disaster could hardly have been anticipated in the light of the medical and pharmacological knowledge at the time, but had a central registry for the collection of adverse reactions then existed the dangers of thalidomide would have

been recognized earlier, and far fewer than 3,000 pathetic cases of phocomelia would have occurred in the world.

Legal Powers

Committees of this kind might have a most detrimental effect on pharmaceutical research by imposing frustrating delays on the introduction of valuable new drugs. It is to be hoped that this committee will avoid this danger, which is certainly well appreciated by it. During the first year of its working it cleared 436 new drugs and preparations, referred 69 for further information, and rejected 15. Thirty-eight other drugs originally submitted have not been proceeded with by the manufacturers. It is also probable that the mere existence of the committee has tightened up standards. Further, at the suggestion of the committee, manufacturers have voluntarily withdrawn certain drugs from the market, have sent warnings to doctors about possible toxic reactions to other drugs, and have amended some of the promotional literature. It is so much better to do things by persuasion and mutual agreement, so far as is possible, than by legal sanctions.

At present the committee possesses no legal powers whatever and is entirely dependent on the good will of the manufacturers and of the medical and pharmaceutical professions, from whom it has so far received the most gratifying co-operation. Thus the Association of the British Pharmaceutical Industry and the Proprietary Association of Great Britain have agreed that their members will not offer a drug for clinical trial until their laboratory tests of it have proved satisfactory to the committee; and, further, they have agreed not to market a drug until the committee has approved the clinical trials to which it has been subjected.

There is, of course, nothing legally to prevent a manufacturer from marketing a drug without the committee's assent, but in that event (it has not as yet occurred) the Ministers have undertaken to inform all prescribers of the fact, and they will draw their own conclusions. Further, should toxic effects result from a drug marketed without the committee's approval, neither its manufacturer nor its prescriber would stand in a strong position in a court of law: these are formidable sanctions.

Legislation will shortly be introduced to consolidate, simplify, and improve the present rather chaotic state of the numerous Acts relating to medicines (the Poisons Act, the Dangerous Drugs Act, the Medicines and Pharmacy Act, the Therapeutic Substances Act, and so forth) and the variety of existing bodies with varying authority over medicines, some reporting to the Home Office, and others to the Ministry of Health, to the Board of Trade, or to the Privy Council. Such legislation will doubtless include the Safety of Drugs Committee, giving it legal power. While circumstances might arise in the future making it essential for the committee to be armed with such power, it is to be hoped that its present freedom of action will not be curtailed by a bureaucratic strait-jacket.

Drug Legislation

The problems and responsibilities of government in assuring the safe use of drugs are indeed formidable. It is so important to see that a law of this nature is executed so as to achieve its high purpose without imposing any non-essential restraint on the pharmaceutical industry or the physician. We have come a long way since the first *British Pharmacopoeia* was published in 1864 in laying down standards for the purity and strength of drugs, and the Food and Drugs Acts of 1938 and 1955 have provided substantial legal protection for the public in these respects. Nor is it any longer permissible to delude the public by advertisements for quack nostrums for the treatment of serious conditions like cancer or venereal disease; and the success of the measures taken many years ago to control the danger of addiction to potent narcotics has been the subject of

almost incredulous envy in countries where such addiction is still a serious problem. These measures have been wholly salutary, but future legislation concerning the safety of drugs is bound to be more difficult, because no drug is ever entirely safe and its safety must be related to the purpose for which it is to be used. For example, a high degree of toxicity might be tolerated if a drug cured or stayed the progress of an otherwise fatal disease, but no significant toxicity would be permissible in a drug used for a trivial condition or if it was shown to be worthless. This brings up the whole question of efficacy and of relative efficacy; and who is going to dogmatize on this? Again, who is going to say that the occasional fatal toxic reactions which may result, for instance, from the use of psychotropic drugs in depressive illnesses are or are not greater than the danger of an increased incidence of suicide if such drugs are forbidden?

Doubtless a committee of experts will advise the appropriate Ministers, and if experts are occasionally wrong they are less often wrong than non-experts. Nevertheless, we interfere with the prescribing doctor's final freedom of decision at our peril in a free democracy. It is easy to set up a sort of pontifical therapeutic Establishment; but Establishments—Aristotle and Galen, for instance—have not always been in the van of progress.

REFERENCES

- Garai, P. I. (1964). In *Drugs in Our Society*, edited by P. Talalay, p. 189. Oxford Univ. Press, London.
 Hill, A. B. (1960). In *Controlled Clinical Trials*. Papers delivered at the Conference convened by C.O.I.M.S., p. 7. Blackwell, Oxford.
 Smithells, R. W. (1965). *Practitioner*, **194**, 104.
 Witts, L. J. (1960). In *Controlled Clinical Trials*. Papers delivered at the Conference convened by C.O.I.M.S., p. 8. Blackwell, Oxford.

Systemic Hypertension and Mitral Valve Disease

H. I. OBEYESEKERE,*† M.D., M.R.C.P.; M. DULAKE,* M.A., M.B., M.R.C.P.;

H. DEMERDASH,* M.D.; R. HOLLISTER,* M.D.

Brit. med. J., 1965, **2**, 441–445

There are many conflicting reports concerning the frequency of systemic hypertension in patients suffering from mitral valve disease, and many theories concerning the relation between the two conditions. We have made a further study of the problem from the case records and necropsy reports of patients with mitral stenosis treated at Hammersmith Hospital. An investigation of patients at present suffering from hypertension and mitral stenosis is in hand and will form the subject of a further communication.

The earliest references in the literature to renal involvement in mitral valve disease were those of Bamberger (1857) and Goodhart (1880), who found a high incidence of mitral stenosis associated with granular kidney at necropsy. Pitt (1887), making an extensive study of necropsy material, was very impressed by this frequent association and suggested that in middle-aged patients mitral stenosis was secondary to hypertension and renal disease. Gibson (1909), describing clinical investigations, stated that the blood-pressure in mitral stenosis is "often below the normal, but even more frequently above it." Cowan and Fleming (1912), while recognizing the rheumatic origin of mitral valve disease, suggested that rheumatism was also responsible for the associated renal fibrosis that occurred in these patients. Carey Coombs (1924) attributed the cardiac and renal lesions to scarlet fever. He suggested that the same attack of scarlet fever which set in motion nephritis and led to progressive renal fibrosis and hypertension also initiated progressive fibrosis of the mitral valve.

Boas and Fineberg (1926) found hypertension (systolic pressure over 150 and diastolic over 90 mm. Hg) in 29% of a series of 135 cases of mitral stenosis of all ages, 50% being in those over 40 years of age. They suggested that the hypertension and granular kidneys often found at necropsy in these patients was due to renal anoxia from a low cardiac output. Levine and Fulton (1928) studied the blood-pressure of 762 patients with mitral stenosis and found the average pressures of patients over 45 years to be higher than those of normal

persons of the same age and frank hypertension to be present in the majority. They suggested that hypertension often proved beneficial by stretching the mitral valves as a result of left ventricular dilatation, and that hypertension by adding to the load on the left ventricle tended to balance the burden on the right ventricle resulting from mitral stenosis. They attributed congestive failure to an imbalance in work of the two sides of the heart.

Then followed a series of reports which denied any association between mitral stenosis and hypertension. Brumm and Smith (1941) found hypertension in only 2% of these patients with mitral stenosis. Horns (1944) found hypertension in only 10% of patients under 45 years, and in 30% of those over 45 years, an incidence no different from that in his controls series. Roseman and Wasserman (1951) gave similar figures in a study of 517 patients, and found no difference between these patients and 2,000 consecutive hospital admissions. Gray (1954) found an incidence of 16.5% of 200 cases of mitral stenosis not significantly higher than that of 200 controls. He further found that hypertension in mitral stenosis is "essential" and not renal in origin. Wood (1956) found a blood-pressure of 160/100 or over in only 3% of his series, and stated that hypertension associated with mitral stenosis was almost certainly a matter of chance.

Present Investigation

The records of 434 patients admitted to Hammersmith Hospital since 1952 suffering from rheumatic mitral valve disease were studied. The diagnosis was made clinically and confirmed in many cases during cardiac surgery or at necropsy. The blood-pressure readings used were the average consistent pressures recorded, and many were basal readings taken during the patients' stay in hospital. Where the patient had been followed for many years the highest consistent recordings were taken. Patients with predominant aortic valve disease were excluded because of the distortion of blood-pressure that is known to occur.

The mean diastolic blood-pressures of patients with mitral valve disease were compared with the diastolic pressures in a

* Department of Medicine (Clinical Cardiology), Postgraduate Medical School of London and Hammersmith Hospital.

† Work done during the tenure of a Nuffield Dominion Travelling Fellowship.