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THE SAFETY OF DRUGS*

BY

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I was honoured by your invitation to deliver this annual lecture in memory of Stephen Paget—a man gentle, altruistic, and courageous—who, by his formidable exertions in the campaign against bigotry and by his foresight in founding the Research Defence Society, did so much to help my profession in their fight against disease in man and the veterinary profession in their similar battle for animals. In Paget's day the contribution of medicines to treatment was a modest one and there was much therapeutic nihilism; but the public is now so impressed with the astounding progress which has occurred that their emotional tide may be on the turn and the same forces which opposed Paget in his day may be on the point—stimulated by the tragedy of thalidomide—of demanding an almost impossible degree of safeguards based on animal experiments.

Voltaire defined medical treatment as the art of pouring drugs of which one knew nothing into a patient of whom one knew less. When he uttered this classical cynicism over 200 years ago it was nearly true, for Voltaire was born only 52 years after the death of Galileo and 37 after that of Harvey, who may be regarded respectively as the fathers of modern scientific thought and scientific medicine. Up to their time thought had been largely deductive, based on the authority of Hippocrates, Aristotle, and Galen.

When he was still very young Galileo became a lecturer at Pisa University and threw a ten-pound and a pound weight simultaneously from the leaning tower to prove that the former would not fall to the ground ten times as fast as the latter. Aristotle had maintained that it would, but neither he nor any of his successors throughout nearly two thousand years had taken the trouble to find out by way of experiment whether what he said was true. The idea of doing so was a novelty, and Galileo's disrespect for authority was considered abominable and he was persecuted by the Inquisition. His conflict with the Inquisition was the conflict between the spirit of induction and that of deduction. Those who believe in deduction as a way of knowledge are compelled to find their premises somewhere—usually in a classical book—jurists from the Roman Law, communists from the works of Karl Marx, Christian Scientists and osteopaths from those of Mrs. Eddy and Dr. Still respectively, medical students from the vast textbooks we write for them, and so forth. Galileo's predecessors had known how the world began and what was man's chief end; the deepest mysteries of meta-

physics and the principles governing the behaviour of bodies were clear to them. Throughout the moral and material universe there was nothing incapable of exposition in orderly syllogisms. As the rising sun scatters the multitude of stars, so Galileo's few proved truths about falling bodies and pendulums dissipated the scintillating firmament of medieval certainties and established doubt.

And science throughout the succeeding years has owed its remarkable progress to doubting all things, even those upon which action has been based. Thus Newton's law of gravitation had reigned so long and explained so much that it seemed incredible that it should stand in need of correction. Nevertheless, as the result of Einstein, such correction at last proved necessary and doubtless this correction will in its turn have to be corrected. The advance of science has been in some respects comparable to the growth of the British Constitution, through the web of which the woof of doubt has usually run. On the whole the opposite has been the case in the politics of other countries, where the deductive method has so often ruled. Here has been the sacred book, the heresy hunt, the solemn excommunication by bell, book, and candle; here one intellectual certainty has replaced another at the expense of a sufficient number of martyrs; and so long as education aims at inculcating dogmas—religious, political, ethical, and medical—fresh relays of martyrs will be necessary for every step in human progress. While I do not suggest that humanity will ever be able to dispense with its martyrs I cannot avoid the suspicion that with a little more thought based on experiment and a little less passionate belief their number might be substantially reduced.

Blazing the Trail

Not only was the scientific method of thought still young in Voltaire's time but for over a hundred and fifty years afterwards medical scientists were concerned not so much with treatment as with anatomy, physiology, pathology, bacteriology, and diagnostic medicine. They had to blaze the trail along which scientific therapeutics could eventually advance; for it is impossible to treat rationally unless one knows how the body is constructed and how it works in health, about the natural history of disease, about the agents of infection, and about what is the matter with the patient. Thus at much the same time as Laennec, the inventor of the stethoscope, was beginning to put diagnostic medicine on a firmer foundation, some 30 million leeches a year were being used by his brother physicians in France in treatment; and doubtless up in Edinburgh James Gregory, famous or perhaps notorious for the powder which bears his

*A slightly abridged version of the Research Defence Society's Thirty-first Stephen Paget Memorial Lecture delivered on November 27, 1962, at University College, London. The full version will appear in the Society's journal *Conquest*.

name, was complacently prescribing 20 grains of calomel—a fearsome dose—to one of the unfortunate lieges; when, about the middle of last century, Virchow in Germany was revolutionizing pathology and altering the whole basis of our knowledge of disease the pharmacopoeias then in use still contained a mass of rubbish, the relics of mediaeval superstition; when Osler published his classical *Textbook of Medicine* about the turn of the century therapeutic nihilism was still so rife that less than 10% of the space in the first edition was devoted to treatment and much of this consisted of pious hopes and vague generalities—“arsenic might prove useful, vaccines should be tried, the general health should receive attention”; and even the Edwardian physician, who often had so much diagnostic skill, had to rely for treatment very largely on bottles of medicine elaborately prescribed, meticulously bottled, elegantly flavoured, and exquisitely labelled, but, as Oliver Wendell Holmes said, “If 80% of them had been poured into the sea only the fishes would have suffered.” It was all still faintly reminiscent of the witches in *Macbeth*—“fillet of a fenny snake, in a cauldron boil and bake.” Our drugs were then, with very few exceptions, derived from substances which happened to occur in nature, from the quicksilver, the poppy, the foxglove, and the cinchona bark. With the exception of quinine they were all symptomatic remedies, and the conception that a drug could be curative, in that it could remove or neutralize the cause of an illness, was still a revolutionary idea.

Therapeutic Progress

Young physicians nowadays, armed with the veritable therapeutic thunderbolts of Jove which the synthetic chemist, bacteriologist, and biological pharmacologist have put into his—often very ungodlike—hands, can have no idea of our sense of the therapeutic impotence even in the 1920s or of how we secretly admired and envied the surgeon—though we tried not to show it—in his often successful Galahad-like jousts with death. And now how different everything is: since 1930 the mortality from gastro-intestinal infections, one of the chief causes of infantile death, has fallen by over 80%, and that from pulmonary infections by nearly 70%, while tuberculosis, meningococcal infections, mastoiditis, and venereal disease all show a similar or greater decline; diphtheria, from which as late as 1940 there were 2,500 fatal cases in England, has disappeared; typhoid, typhus, tetanus, cholera, plague, yellow fever, smallpox, whooping-cough, and poliomyelitis can be prevented; many tropical diseases such as malaria have been brought under control; and the lives of patients suffering from diabetes and pernicious anaemia are preserved. The list is far from comprehensive and makes no mention of the relief of suffering which the purely symptomatic use of modern drugs confers.

Doubtless the all-round improvement in living conditions has greatly contributed to these remarkable results which have since 1930 increased the expectation of life of men and women in this country by about ten years, but the use of potent new drugs has been an even more important factor. To take tuberculosis alone as an example: the decline in its mortality from 1900 to 1945 was at about 3% a year in Britain and the United States apart from the years of the two world wars in Britain. This 3% annual decline was almost entirely due to the improvement in social conditions; after 1948, when effective antituberculous chemotherapy became available,

the decline in mortality abruptly accelerated to an average of 15% a year in both countries and if this continues—and there are good grounds for expecting it to do so—tuberculosis as a cause of death in this country will have virtually disappeared by 1975.

Animal Research

The agents responsible for the advances which I have enumerated have practically all been discovered as the result of research on animals, tested for toxicity on animals, some of them standardized for the market by means of tests on animals, and many of them—the bacteriological products—have been prepared from animals themselves. I wonder, if most anti-vivisectionists actually saw a person suffering from lockjaw or rabies, or a little child suffocating from laryngeal diphtheria—all most terrible spectacles—whether they would persist in their campaign of persuasion to make people refuse the protective inoculations. The late George Bernard Shaw—a protagonist of vegetarianism, a violent anti-vivisectionist, and a shrewd critic of the medical profession—did not martyr himself on the altar of his principles when he developed pernicious anaemia by refusing treatment by liver which was entirely discovered by Minot's experiments on dogs. In consequence he lived to a ripe old age but made no acknowledgments, taking by injection the products of the Chicago abattoirs which he scorned as food.

The scientific attitude which has made these great advances possible is still, however, unnatural to man and only employed by a minority of people who themselves confine its employment to a minority of problems. “Most people,” as Samuel Butler said, “would rather die than use their brains.” The majority of our opinions are mere wish-fulfillments like dreams in the Freudian theory and the mind of the most rational can be compared to a stormy ocean of passionate convictions based upon desire upon which float perilously a few tiny boats carrying their cargo of scientifically tested beliefs. Nor is this entirely to be deplored: life has to be lived and time is too fleeting to test rationally all the beliefs by means of which our conduct is regulated. In regard to drug treatment, however, it is much to be desired that the art should be tempered by a wholesome dose of scientific reason.

Over-prescribing

In respect of treatment, however, this is just what many patients and a few doctors do not seem to want. Like Lot's wife, they are all too prone to look back, longing to return to the past with its ritual and its magic; and when disease arises with its toxic and frightening influences the primitive man creeps out of the cave in which reason has shamefacedly tried to conceal him, whimpering and crying for his witch doctors, his totems, and his charms. Thus it has to be confessed that there is a great deal of over-prescribing of medicines nowadays. During recent years there have been several analyses of the prescriptions issued on Form E.C.10 under the National Health Service, whose total drug bill now reaches the formidable figure of over £100m. a year.

Such studies stimulate the reflection that it is strange when we can do so much for patients that such a great deal of time and money is still spent on the prescription of the Edwardian bottles of medicine to which I have already adverted. We may laugh at the witch doctoring

of the past—the “eye of newt, and toe of frog”—but our smile should be a wry smile and not one of smug self-satisfaction. There are those who say, rather cynically, I think, “but the public demands a good bottle of medicine, and after all it has a great psychological effect.” Yes, but the public demands all sorts of mumbo-jumbo which has a great psychological effect. What we condemn in others we should not so complacently condone in ourselves, and we should attempt more than we do to educate the public in rational therapeutics instead of pandering to its primitive desires, even though the desire to take medicine seems to be the chief thing which differentiates man from the lower animals.

There are many causes for over-prescribing: the insistent demands of patients for medicine, the fact that some doctors are very ill informed, the size of some lists under the National Health Service, and the formidable and highly skilled advertising of the pharmaceutical industry—some of which is subject to justifiable criticism. Nevertheless, the mere fact that drugs are sometimes over-prescribed and misused, or that they sometimes give rise to serious toxic effects—for there are no therapeutic roses without their thorns—is no argument for their wholesale condemnation.

Rise in Costs

The increased cost of drugs to the National Health Service has steadily risen from £35m. in 1949–50 to over £100m. now. This has been due not so much to their overall increased price as to the greater number of prescriptions written and to the much greater use of more expensive drugs such as antibiotics, which account for about a quarter of the total bill. The cost has been great but the savings have been much greater: as we have seen, there has been a vast saving in mortality rates which is well documented; but the tremendous saving to the national economy in diminished morbidity, absence from work, and decrease in the number and duration of admissions to hospital is more difficult to estimate; but, taking tuberculosis alone, the annual saving resulting from the use of drugs is estimated at £55m. a year, about half the cost of the total drug bill under the Health Service. To put the cost of drugs which have conferred such immense benefits into perspective we should remember that if expenditure on them is £100m., that on all forms of gambling, on alcoholic drinks, and on tobacco is about £1,000m. for each. Further, in all countries of the Western world Britain spends the least on drugs at 16s. per head per annum, Holland 22s. 2d., Sweden 25s. 8d., Western Germany 26s. 1d., U.S.A. 33s., Italy 47s. 5d., and Belgium 55s. 4d. Gross excess elsewhere does not, of course, justify over-prescribing here.

The pharmaceutical industry, which has recently been under constant attack, has been largely responsible for the therapeutic advances of modern times. The industry in Britain is at present flourishing, principally because of its export business, which has risen in the last 20 years from £5m. annually to £50m. now. We must beware not to kill the industry—the goose which has laid so many golden therapeutic eggs. Scientific discovery is a potent form of economic energy and there is nothing wicked in making a profit, provided it is not excessive, though some people seem to think so. It is interesting to note in this connexion that in 45 years since the October revolution the State-run industry in

the U.S.S.R. has not produced a single new drug of importance.

Though the physician is still finally responsible for the drugs which he prescribes he has not for a long time gathered them himself from the hedgerows by the light of the moon and prepared them into medicines. He very soon delegated this duty to the pharmacist. Recently the great increase in the number of potent synthetic drugs and the corresponding decrease in the use of the naturally occurring galenicals has seen a further inevitable delegation of responsibility by the pharmacist, tinged with a nostalgic regret, to the pharmaceutical manufacturer. How are these new drugs discovered? How is their toxicity evaluated? How is their strength assayed? How is their dose determined? I wonder if anti-vivisectionists—the majority of whom make use of drugs—have ever considered these questions.

Drug Control

Professor Walter Perry in a recent paper has sketched the history of drug control. The earliest attempts at this were the herbals. In the first century Dioscorides provided detailed descriptions of plants, minerals, and animal matter to help physicians to recognize and use them. Though the physician's head might be cut off if the consequences of their administration were dire, he was not then summoned under the provisions of any Act. From the herbals grew the pharmacopoeias, and the London and Edinburgh pharmacopoeias were essentially herbals given control authority through the Royal Colleges of Physicians. Then came the national pharmacopoeia of 1864, and now there is even an international pharmacopoeia. There has thus been a progressive widening in the uniformity of drug control, so that nowadays a patient may have some confidence that he will be supplied with the same agent whether he purchases it in New York, Paris, Ankara, or Tokyo. In more spacious days it sufficed if he always bought his infusion of digitalis leaves from Mistress Page rather than from the rival Mistress Ford down the street, whose brews might differ from one another like the strength of a cup of tea in different houses.

There will always be two main uses in drug control—for great numbers of tests on experimental animals: firstly, to investigate new chemicals for their possible therapeutic value; and, secondly, to control the potency and toxicity of certain established drugs on a batch-to-batch basis.

It is true that most drugs can be standardized by physical or chemical methods, but biological tests—that is, the observation of the pharmacological effect of a drug on living animals or their isolated tissues—are necessary for bacteriological products, such as vaccines, antitoxins, and sera; for some hormones, such as chorionic gonadotrophin, corticotrophin, oxytocin, vasopressin, and insulin; and for digitalis. Every batch of such products produced requires biological testing, and the accuracy of the assay depends on the number of animals used. Some idea of the number of animals required may be got from the fact that in Britain some 50 batches of insulin are tested a year, involving some 400 mice per batch or some 20,000 mice a year. The potency of the unknown batch is estimated by comparing its hypoglycaemic effect on the mice with that produced by a standard preparation. How, I wonder, would a diabetic anti-vivisectionist

prefer this standardization to be done? Would he care to subject himself to the probability of a hypoglycaemic shock or diabetic ketosis every time he got a new and untried batch of insulin? Or would he, like the Nazis, suggest the use of criminals, lunatics, or political opponents? Even then there would hardly be 1,077,000 of them, for this is about the number of experimental animals necessary each year for the biological assay of drugs.

The introduction of new therapeutic agents to medical practice is preceded by long and laborious research exercises which may fail at many stages. Great numbers of chemicals which seem likely to affect a particular pathological condition have to be screened by organic chemists. From 1 in 60 to 1 in 100 of those screened are found worthy of further study: those selected are then subjected to detailed toxicological and pharmacological investigation on animals. Perhaps from 1 in 20 to 1 in 40 of these are then considered worth clinical trials in human beings and only a few of those 30 chosen will ultimately be marketed. Thus in 1958, 114,600 compounds were tested but only 44 entirely new chemicals—I do not refer to the innumerable compound pharmaceutical preparations—were put on the market. In recent years the number has varied between 40 and 50.

All new drugs require acute toxicity-testing, which consists of the administration to animals of large single or divided doses over a short period of not more than 24 hours; almost all of them also require chronic toxicity tests, the length of which varies according to circumstances from a week or two to perhaps two years. The tests should also reveal the presence or absence of a species difference, so that a variety of animals should be included in the trial, and if a species difference is noted the application of the drug to man must be the more cautious. The pharmacological screening and toxicity testing necessary to put 20 new chemicals on the market a year involves the use of about 1,200,000 small rodents and 16,000 cats or dogs. Cats and dogs are relatively expensive and difficult to procure, yet as the result of anti-vivisection propaganda thousands of stray unclaimed dogs and cats have to be destroyed by the police instead of being made available for research. This senseless waste only results in more dogs and cats being sacrificed: to revoke this state of affairs should now be one of the main activities of the Research Defence Society.

Toxicity tests are also essential for each new batch of certain established drugs. Such routine tests for freedom from abnormal toxicity are expected to be negative, and the animals used for them are usually unharmed and often used repeatedly. Yet each time they are used constitutes an "experiment" under the Act. The best example is the pyrogen-testing of such common intravenous solutions as saline or glucose, which is done on rabbits—about six rabbits being used for each batch. A firm making 250 batches a year will conduct some 1,500 experiments, perhaps on a colony of 30 healthy rabbits which remain normal while they get one intravenous injection and have their temperatures taken for a few hours each week.

In the great majority of instances the tests of new drugs by reputable manufacturers are scrupulous and complete. Occasionally, however, drugs are released for clinical use without sufficient information being made available. As Noel has said in a recent article in the *Lancet*: there are firms who still reduce the test period of their investigations and the numbers and species of

animals in them. Their results pass muster, as doctors are unfamiliar with the basic requirements, and when they see that "the results of chronic toxicity tests are negative" they accept them to indicate the safety of the drug. There is thus a need for the setting up of official or semi-official national and international bodies, perhaps under W.H.O. at Geneva, to examine such results and to pronounce on their validity, to lay down minimal standards for all new drugs, and to ensure their similar nomenclature. Such minimal standards would not of course prevent any country from improving on them if thought to be necessary.

Centralized Office of Information

Further, we do not as yet have adequate machinery to ensure the fullest possible collection of data about the clinical toxicity of drugs. We have no centralized office to collect information on all supposedly toxic reactions from drugs which may have passed stringent initial tests for toxicity, clinical safety, and usefulness. Only with organized accumulation of information in this country and abroad about efficacy and toxicity can we plan the necessary control measures based on factual knowledge. Professor A. G. Macgregor has recently pointed out that in this country we are tending to proliferate committees to undertake the important task of drug evaluation which may overlap each other and often consist of much the same group of dedicated and overworked scientists, doctors, professors, and pharmacists. At least four separate committees have been established recently to supervise the introduction of new drugs and to detect their toxicity, by the British Medical Association, the Medical Research Council, the Pharmaceutical Industry, and the Ministry of Health through its Standing Medical Advisory Committee. It is surely necessary to have some single authoritative body. Professor Macgregor goes on to point out that "the present ferment of committee and legislative activity is being conducted not for the reasons for which it should have been initiated—because we should be rational, scientific, and informed about the use of drugs—but because of the emotional reaction to the terribly tragic consequences of the administration of thalidomide to pregnant women, which could hardly have been anticipated in the light of medical and pharmacological experience at the time." Nevertheless good may result from this tragedy, and we should remember that

"Sweet are the uses of adversity,
Which like the toad, ugly and venomous,
Wears yet a precious jewel in his head."

The effective interchange of information must be established on an international basis, and the establishment of informative machinery of this degree of complexity will require considerable resources. Senator Humphrey, who is sponsor of amending legislation to tighten up the conditions under which drugs are released for clinical trial in the United States, has said, "An awful lot of people believe in economy and at the same time believe in miracles. The two seldom go together, and if you want improvement you have got to pay for it."

Even if control measures are perfected there will always remain inherent risks in the taking of all drugs, since, no matter how meticulous the preparatory work of the pharmacologist and clinician, there is no ultimately complete substitute for many years of routine clinical experience of their use in thousands of

patients. No matter how thoroughly a new drug has been tested in experimental animals, possible species differences must never be forgotten in assessing its precise effect in man. As Mr. Hanbury, of the British Pharmaceutical Industry, has recently said, "there are innumerable examples of drugs of the utmost value, even penicillin itself, which have brought life and health to millions of people but serious trouble to the few. Vaccination against smallpox involves a grave risk to a

tiny minority, considered worth taking for the good of the majority. Even the use of the homely aspirin is by no means devoid of danger. Those who say that nothing short of complete safety will suffice are crying for the moon, and if their clamour were taken at its face value stagnation would be the sequel. The public which demands therapeutic progress must be prepared to accept some risk, though its degree and extent can be minimized by intelligent safeguards."

MISPLACEMENT OF THE ELDERLY IN HOSPITAL

A STUDY OF PATIENTS ADMITTED TO GERIATRIC AND MENTAL HOSPITALS

BY

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The need for development of hospital services for old people in relation to the growing number of persons of pensionable age is now widely known (*Lancet*, 1961). There is an increasing call for hospital accommodation, and very often the demand for beds exceeds the number available. Many facilities for the care of the elderly have been provided largely in advance of the assessed requirements, and consequently their value has been lessened by extending these facilities to patients who could more suitably benefit from alternative care and accommodation. A major obstacle in the development of these urgently needed services is the frequency with which old people are sent to the wrong hospital.

Evidence for Misplacement

Misplacement of the elderly in hospital has long been attributed to the lack of criteria for assessing the disabilities of old people and planning their disposal. The mental and physical changes of ageing cannot readily be separated, so there is difficulty in deciding whether a patient requires psychiatric or geriatric care. In old people the evaluation of cases where physical or psychological factors coexist is particularly difficult.

It has been shown (Affleck, 1947; Robinson, 1950; Kay and Roth, 1954; Kolb, 1956; Tewfik, 1956; Cross *et al.*, 1957; Cosin, 1958; Adams, 1959; Tec *et al.*, 1960; Townsend, 1962; McKeown, 1961; McKeown *et al.*, 1961) that in routine geriatric and mental hospital practice old people are often clearly misplaced. Many beds are occupied by patients who should have been admitted to a unit more fitting to their particular type of disability. Too many geriatric hospitals are filled with long-stay demented patients. Conversely, patients are being sent to mental hospitals when their sole psychiatric disorder is delirium due to severe physical disease. Between these extremes misplacement is seen in the medical wards where patients are admitted for investigation of physical complaints which may not be recognized as hypochondriacal concomitants to a primary depressive illness (Sargant, 1961), and in mental hospitals where debilitated and tractable old people who can only technically be called psychotic are admitted for chronic sick care. It is not in the best interests of an old sick person to be transferred from unit to unit, so that mental hospitals commonly retain patients who ought to be in

geriatric units, and, conversely, general and geriatric hospitals keep those who would be better placed in mental hospitals.

It was felt worth while to study the effects of misplacement of the elderly in hospital from two contrasting approaches: the first dealing with assessment of disabilities and the second with the consequence of these disabilities in respect of the type of hospital care the patient is given.

Using techniques previously described (Kidd, 1962) it has been shown that misplacement occurred to a considerable extent both in the mental hospital and in the geriatric unit serving the city of Belfast. Assessments of disability from physical illness and psychiatric illness respectively were made on 100 patients aged 60 and over admitted to each unit. The ratings were based on the possibility of clinical improvement, and by their use it was possible to evaluate the relative severity of the two types of disability. This allowed classification of each patient into one of four groups (Table I).

TABLE I.—Distribution of the Two Hospital Samples by Assessed Categories

	Mental Hospital Series (n = 100)	Geriatric Unit Series (n = 100)
Mental	57	20 { misplaced
Mental-physical	19	14 { 34%
Physical-mental	11 { misplaced	29
Physical	13 { 24%	37

The patients in the mental hospital series who were assessed as physical and physical-mental were medical cases and are therefore designated as "misplaced in choice of hospital." They account for 24% of the series. In the geriatric unit, patients assessed as mental and mental-physical were psychiatric cases and are also designated as "misplaced in choice of hospital"; these accounted for 34% of the total geriatric series. Thus it is apparent that a substantial proportion of the patients in each hospital were misplaced and would have been more appropriately placed in the other.

Obviously the most important factor in misplacement was the presence of overriding physical illness in the mental hospital patients and predominantly psychiatric illness in the geriatric unit patients. Analysis of the cases, however, revealed concomitant characteristics of