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Inaugural Plenary Lecture

Drug analysis — Why?*

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Introduction

As we are gathered in Brussels to take part in the Second International Symposium on Drug Analysis it may seem rather strange to be asking whether we need to analyse drugs at all. There are, however, those who nowadays suggest that, with all the safeguards built in along the route, there is no need to analyse a final product. We should therefore, before embarking on what promises to be a very exciting and fruitful meeting, carry out a little self-inspection and self-criticism to help establish whether or not we are all working to useful purpose.

Judging by this Symposium alone there must be a great many people engaged in the analysis of drugs for one purpose or another throughout the world. The list of abstracts submitted up to the first of January of this year indicated that 173 intentions to present papers had been received and these emanated from 31 different sovereign states. It would be cynical and wholly unworthy to suggest that the submission of a paper is often the only means of providing a means to attend, so I shall dismiss that out of hand. I am quite convinced that the quality of work we shall be hearing presented at this Symposium will belie any such base suggestion.

To determine the real reasons why it might be necessary to analyse drugs I feel that we should delve a little deeper and begin by considering how interest in analysing drugs might have arisen in the first place. To do this we must remind ourselves that until the beginning of this present century drugs were largely natural products, principally herbal in origin. Such products, according to source, time, method of collection, and subsequent preparation can vary considerably in potency. Whereas this might be of little concern with some of the milder materials, it is obvious that it could be of considerable importance for natural products that are very potent. A single example will suffice to illustrate the point.

From the Quintessence to the Chemical

In his book "Confessions of an English Opium-Eater" the man of letters Thomas De Quincey [1] described in a footnote the dilemma of a friend of his, a surgeon, who was suffering from a lingering and fatal malady. Yet he had a family to support and had to

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continue working for as long as possible. Because of his professional knowledge he saw the necessity of reducing the daily dose of opium that he took to alleviate his pains to a minimum. I now quote the words used by De Quincey: "But to do this he must first obtain the means of measuring the quantities of opium; not the *apparent* quantities as determined by weighing, but the *virtual* quantities after allowing for the alloy of varying amounts of impurity." With the knowledge available at the time (about 1820) De Quincey's friend was unable to form such an assessment. He did, however, achieve a uniform method of extracting the opium so as to give a fairly constant potency.

The gradual change from the use of natural products in their entire state to either purified extracts from those products or to synthetic chemically-produced materials can be said to have been taking place between the time of Paracelsus who lived in Basel during the first half of the 16th century, to that of Ehrlich, to whom the award of a Nobel prize in 1909 was a fitting reward for his remarkable researches and breakthrough during the first decade of this century. This period has been described as that leading from 'Quintessence to Chemical' and has been fascinatingly reviewed by H. J. Barber [2].

This transition from the quintessence to the chemical stimulated a very considerable amount of interest in the analysis of natural products to determine, as De Quincey had said one hundred years earlier, not the apparent quantities as determined by weighing but the virtual quantities after allowing for the alloy of impurity.

The growing awareness of the need to analyse drug substances themselves was also apparent before any synthetic materials found regular use in medicine. Since this Symposium is being held in the year 1986 I would have liked to have quoted an example from just 100 years ago. I note that the first edition of the Japanese Pharmacopoeia was published in 1886, but unfortunately I cannot read Japanese so I am unable to look for a suitable example among its pages. Perforce then I have had to turn to the British Pharmacopoeia published in 1885 [3]. The monograph on morphine hydrochloride (or hydrochlorate as it was called) was very different in form from that which we expect in a Pharmacopoeia today. The bulk of the monograph gave detailed procedures for the preparation of morphine hydrochloride from opium itself; this would surely have been of considerable assistance to De Quincey's friend had it been available to him! There is a section however called *Characters and Tests*. The material is described as a powder or as thin prisms with a silky lustre. Its approximate solubilities are given as are some tests to demonstrate the presence of chloride and various colour reactions indicative of morphine. A single sentence indicates: "Ignited with free access of air, it burns without leaving any residue". What legal disputes such a statement would give rise to today! Finally there is an assay and I think it worth telling you of it in full so that you may, during the remainder of this week, reflect on just how far we have come in the last hundred years. It reads: "Twenty grains of the salt dissolved in half an ounce of warm water, with ammonia added in the slightest possible excess, gives on cooling a crystalline precipitation which, when washed with a little cold water, and dried in a water-bath weighs sixteen grains." If anyone wishes I can give them a copy of that method expressed in S.I. Units.

It should be noted in these examples quoted from a century ago that two fundamental points are missing — two points we would insist upon in any requirements set today. The first of these is that the test for residue on ignition demands complete absence as a criterion of acceptance: "without leaving any residue". The second is that the assay results are expressed without any tolerance of acceptance: "the crystalline precipitate weighs sixteen grains". This latter statement in particular shows an absolute faith in the

correctness and the precision of the analytical result which I hope is not shared by anyone present today. We have developed enormously in technical knowledge during the past hundred years; I hope we have also developed philosophically to the extent that we all recognise the frailty of the results we obtain, even when they are convincingly displayed in digital fashion to several 'significant' figures.

The increase in use of classical analysis to quantitate and define materials used in medicine, together with the increase in use of materials of synthetic origin and of increasing complexity, is evident from a study of pharmacopoeias of various countries issued between 1900 and 1950. Shortly after this period one can see the exciting beginnings of a completely new era in the analysis of drugs based on the introduction of new concepts of analytical methodology that found no reference in the classical analytical textbooks of the time. The introduction of complexiметric and non-aqueous titrimetry in the early 1950s, of gas liquid chromatography in 1952, of thin layer chromotography in 1956 together with the increasing applications of ultra-violet and infra-red spectroscopy during this period, can all be followed in the pages of any national pharmacopoeia that was being published regularly during this period.

This brings us to the early 1960s and at that time any regulatory interest in the quality of drugs rested almost entirely on the pharmacopoeias. From this generalisation I should exempt the activities of the Food and Drug Administration in the United States and the Control of Biological Materials that was exercised by the so-called 'Therapeutic Substances Act' in the United Kingdom. No doubt there were similar enactments in other countries, but their effect on the great majority of materials used in medicine at the time was of little consequence.

Quality Assurance and Good Manufacturing Practice

The single word thalidomide epitomizes the far-reaching changes that then came about. For the first time, perhaps, the man in the street and hence the politician became concerned with drugs. This has led to a much broader sense of the quality control of medicines. What used to be the Analytical Department in a pharmaceutical manufacturing company became the Quality Control Department and many of its interests and concerns became taken over in the concepts of Quality Assurance, Good Manufacturing Practice, inspection and of licensing.

In the European Community of countries directives have been issued to ensure that the legislation in each member state shall provide for the comprehensive examination of intended drug materials before they are allowed to enter the market. Mutagenicity, carcinogenicity, toxicity, foetal toxicity, effect on reproductive function, pharmacodynamics and pharmacokinetics are among the properties to be studied and the material must be unequivocally characterised with respect to the substance itself and the amounts of impurities that are likely to arise during the course of validated production processes.

Certainly if these extensive biological tests are to be carried out on a new material it is obvious that that material must first be characterised without any possible doubt. It would indeed be a very expensive business to have carried out such extensive testing on a material that was later shown to be something other than was originally thought. So, here at least there is a definite need for drug analysis in the most searching possible way. It will be apparent also that during these extensive biological tests there will be a need for sensitive methods of detection and determination of both the drug substance itself and of its metabolites in body fluids and tissues. Such investigations are, however, usually

required only during the initial stages of drug development. After such extensive study and validation, should we bother with subsequent routine examination on a batch to batch basis and if so, why? The material will have been manufactured by an established and validated process using raw materials of known provenance and by personnel of established and acceptable reputation. Each batch of material produced will have been fully documented at all stages during production. Notwithstanding these controls and assurances it would be a rash manufacturer indeed who then proceeded to market the product without analytical results to confirm its suitability.

Perhaps the most extreme example of this situation is exemplified in the case of sterile materials that have been prepared by fully validated and controlled processes so that sterility of the final product is beyond doubt. The question has frequently been debated, particularly in recent years, as to whether or not there is any point in carrying out a formal test for sterility. The scientific community as a whole is almost unanimous in its recognition that this imperfect test is something of an anachronism in present-day manufacturing conditions. Nevertheless I know of very few manufacturing concerns who would actually agree at the present time *not* to carry out such a test. In the unfortunate event of something actually going wrong and a non-sterile product being produced, the final damning thrust in a courtroom would be the need to answer "No" to the question "Did you carry out a sterility test?" If even in this extreme case the final testing is not to be abandoned, how much more so should it be retained for the generality of analytical examinations?

At a later stage, once the product has entered the open market, there should be every opportunity given for external independent challenge. The possibility of deterioration on storage, of criminal substitution, of counterfeiting and of innocent mistake must all be considered. In some areas of the world these possibilities are, regrettably, very much more likely than in others and circumstantial evidence suggests that they are on the increase. They should, however, be guarded against everywhere. It is for this reason that sound, publicly available specifications are an essential part of the regulatory control system, notwithstanding the advanced procedures of licensing and inspection in many countries.

Improving Drug Quality

Let us turn for a moment to a quite different aspect of analysis and one that is not often considered or given much credence. It is my firm belief that over the last twenty years the very existence of searching analytical methods has contributed quite considerably to an improvement in the general quality of drugs. We are all familiar with the adage that 'quality must be built into a product — it can never be *analysed* into it'. This is of course quite true when one is considering an individual batch of material. If, however, consideration is turned to the long-term development of a process, I believe that analysis has a very large part to play in the improvement of that process. To purify a material and remove excessive impurities one must first recognise that they are actually there and what their nature is. In the past this was not always done.

I would like to illustrate this point by referring to a case that might be well known to some of you and that relates to pethidine hydrochloride. A pharmacopoeial description of this material appeared in 1948 and this was based on a combination of identity tests, not very specific if taken in isolation, but together giving a reasonable assurance as to the nature of the material. These were supplemented by a fairly precise but non-specific

assay and a narrow-range requirement for melting point. This specification was regarded as a reasonable indicator of satisfactorily pure material for some twenty years and the requirements were readily met by material that was available at that time from a number of sources. In 1970, however, Grew [4] published a report on a gas chromatographic investigation of various samples of the substance obtained from different sources. He showed that, far from being the homogeneous material implied by the earlier specification, it might contain at least two impurities, one being up to a level of approximately 9% w/w. These impurities were closely related compounds and their presence in varying amounts probably, in this particular case, had little effect on the overall efficacy and usefulness of the material. Nevertheless it was an affront to analysts to find that they had been misled into supposing that they were dealing with a fairly pure material when in fact the actual content of pethidine hydrochloride itself might only be of the order of 88%. Once the presence of these impurities was recognised it became a relatively simple matter to introduce modifications to purification procedures in order to eliminate the impurities or at least reduce them to quite low levels. Hence the continued analysis of products and the application of newer techniques of analysis as they become available is essential on a regular and continuing basis. What is thought to be "pure" today will certainly be shown, as your researches into new analytical techniques continue, to be not so pure tomorrow.

Technical Capability and Realism

What I have just said might, of course, imply that I believe that material should be purified so as to reduce all impurities to the lowest conceivable levels. Such is far from the case. We have now reached a stage of development of analytical techniques — and this will undoubtedly be demonstrated to us time and time again during the course of this Symposium — at which extremely low levels of impurities may be separated, identified and quantified. Simply because analysts have the power to reach such conclusions, it does not mean that regulatory authorities should demand that levels of purity concordant with analytical possibilities be met.

In this connection I must confess that, on a purely personal basis, I have some fears for the future. Can we be sure that generations of regulatory bureaucrats yet to come will show even the same degree of enlightenment in heeding scientific judgement as is the case today. On the one hand, there is a tendency to analyse to extreme limits because the power is available, and on the other, to regulate and set requirements because the power is there also. There is also a tendency for generalisations to be promulgated as guidelines to be applied in all cases unless appropriate justification can be provided. Such generalisations are undoubtedly convenient and potentially time-saving, but there is a danger that what constitutes 'appropriate justification' can be interpreted differently from one place to another, or from one time to another. Ideally every individual case should be considered on its merits and, above all, the principal reason why we analyse drugs should always be kept in mind: that is, the ultimate welfare of the patient who will take them.

We must therefore make it our business to be ever vigilant that *requirements* for finished products should be based on what can scientifically be demonstrated to be *necessary*, rather than on what can be scientifically demonstrated to be *achievable*. A number of delegates at this Symposium will probably remember a true story that I sometimes tell in which I quote a statement made to me after the F.I.P. Congress in

Dublin, 1975, that "you analytical chemists are finding less and less these days of things that were hardly even there in the first place".

Biological Tests and Biotechnological Products

But so far I have largely directed my remarks to the physical and chemical analysis of drugs. In an overall consideration of drug analysis, however, we must not lose sight of the considerable importance, still indispensable in many areas, of biological and microbiological examination of drugs. In a Symposium such as the present one, concentrating as we are on extending the frontiers of investigation into chemical and particularly physical techniques of analysis, we might fall into the trap of believing that this is all that is required to demonstrate the integrity of drugs. A single example will, I hope, suffice to demonstrate that this is far from the case. I happen to believe that it is probably of much greater significance, for the patient's welfare, to determine the degree and nature of microbial contamination of a preparation than it is to establish whether the active ingredient contains 0.05 or 0.1% of impurity, or whether it is present within limits of ±5%.

With many materials, too, it is not possible to be assured of the true nature by chemical and physical means alone or even, possibly, at all. In such cases resort has often to be made to assay procedures based on inducement and measurement of a biological response. A constant challenge to those who analyse drugs must, therefore, be to develop procedures, whether based on physico–chemical concepts or on the use of isolated biological systems, that will reduce, and eventually eliminate entirely, reliance on tests carried out on sentient animals.

Another area of challenge in the analysis of drugs is offered by the emergence of so-called biotechnological procedures, particularly of recombinant DNA technology. Consideration of the nature and extent of the analytical examination that will be required for such materials is being debated in many fora throughout the world at the present time. I venture to suggest that, notwithstanding the most rigorous and exacting requirements for validation of production processes, the final analytical examination will be no less severe and demanding. In any uncharted area this must be so. But shall we have the wisdom and the courage, as knowledge grows and as the depths and shallows of the uncharted region become illuminated, to review and relax requirements as far as seems possible?

What, Why and How in Analysis

The philosophical consideration embodied in these thoughts is well illustrated by yet another example from the past. During the early years of the present century everyday materials containing considerable quantities of arsenic were prevalent: paints, dyestuffs, sheep dips, crop sprays, fly papers and many others. Accordingly arsenic was a frequently encountered impurity in many other materials, including drugs. Pharmacopoeias of the first half of the century consequently paid exaggerated respect to the need to test for arsenic at quite low levels. It was not until about 1950 that the need for such testing in the very changed environment then prevailing was questioned. I recall that it was once calculated that, with a limit of 1 ppm of arsenic in a certain dyestuff, it would be necessary to take the mixture that was coloured with it for several thousand years in order to absorb a cumulatively toxic dose.

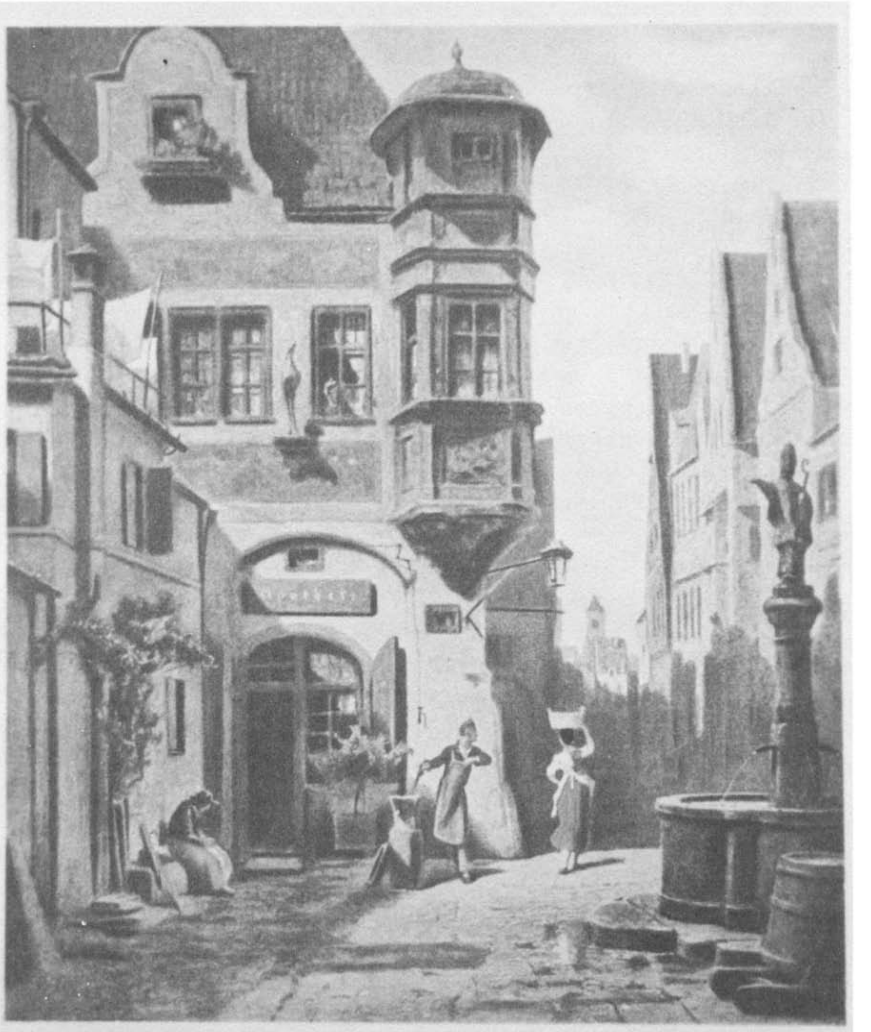
So it is essential, from time to time, to pause for a while to question what we are doing, and why we are doing it. I would even add to this list the question, how we are doing it. We all know of the experts in a particular technique who become so engrossed in its power and, to them, perfection, that they devote themselves to that technique to the exclusion of all else. It is probably necessary that such devotees exist so that all techniques available to us can be developed to their apogee. But for the majority of us it is important to continue to consider, in a spirit of self-criticism, why we are analysing and how we are analysing.

We should also consider that the purest of drugs compounded into the most elegant of dosage forms might still provide a medicine that is of little value to the patient. This may arise, as we all know, from injudicious formulation that could impair or possibly enhance the availability of the active ingredient to the patient. In routine batch to batch production quite minor changes might have an effect on this factor. Analytical procedures that might enable prediction of such impairment — or enhancement — are thus essential in a number of cases. As with so many of the other factors that we have been considering, the more potent the drug the more significant may this aspect become.

Concluding Comments

In summary then, I would stress again that we need analysis of drugs for a wide variety of reasons. We need it to characterise the true nature and degree of homogeneity of new materials before they are subjected to the intense barrage of screening by biological and clinical methods that must precede their adoption as drugs. We need it, with methodology affording the utmost sensitivity, to evaluate levels in body fluids and tissues in support of those biological examinations. We need it to provide the ultimate assurance on a batch by batch basis of newly manufactured material. We need it to provide an assurance, or at least an informed prediction, of bioavailability. We need it on the part of the independent control analysts to guard against error, deterioration and falsification. We need it to recognise undesirable levels of impurities thus leading, in necessary cases, to an improvement in the quality of drugs in general.

To underline just one of these reasons as to why we need analysis, I would like you to consider a favourite picture of mine — a picture that was painted perhaps not so far from this city of Brussels, at about the time when De Quincey's friend was concerned with the strength of his opium. We see an assistant at work outside an apothecary's shop. He is blending materials in a mortar in true pharmaceutical fashion. It is difficult to say whether he is blending in order to get a homogeneous mixture or whether he is grinding to reduce the particle size of the material so as to ensure bioavailability. It seems reasonable to suppose that the formula to which he is working has been well documented and is there in the shop having been approved by the master. It is also reasonable to suppose that the master will from time to time come to the door of his shop to inspect what is going on. But what is going on at the precise moment captured in this charming scene is that the worker's mind has wandered in the direction of a lady passing by and, dare I say it, wandered in a direction that is equally valid today as it was all those years ago. And because his mind has wandered some enthusiasm for the mixing or the comminution has been lost, with the result that the product he is preparing will show a non-uniform content or perhaps will be non-bioavailable. Yet it will find its way into the final containers and will be labelled and sold in the shop and ultimately administered to a



-1885): *De verliefde provisor* ★ *L'aide-pharmacien amoureux*
The love-sick dispenser ★ *Der verliebte Provisor*

defenceless and unsuspecting patient. A defective product will thus have been produced and will have escaped the whole net of quality assurance schemes, with possible fatal consequences.

And that is why we have to analyse our drugs.

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