THE INVESTIGATION OF TOXIC HAZARDS *

BY

M. W. GOLDBLATT

(Imperial Chemical Industries (Dyestuffs Group))

The purpose of this paper is to draw the attention of medical officers in industry who are responsible for the health of workers engaged in operations involving the use or manufacture of toxic materials, to the importance of a measure of fundamental or elementary knowledge of the measures that must be taken to discover the dangerous properties of such materials.

A high proportion of the work of industrial doctors has to do with matters of organization, routine examination to determine the presence of every-day disease, accident surgery, ventilation, lighting and heating, canteens, transfer to and from particular work, sickness absence and so on. Whilst all such activities can be regarded as scientific activities, there is at least some doubt as to how far the average doctor finds himself in a state of confidence when expressing views on matters somewhat outside the sphere of general doctoring.

We have all in recent months seen publications on so important a matter as sickness absence in which conclusions alleged to be based on statistical analysis serve merely to show that the basal elements of scientific observation are all too little appreciated. It seems to me that industrial medical men must realize that in some fields they must start *ab initio* and not assume that an opinion can be given merely by virtue of the fact that the matter has something to do with health or sickness.

Many of us have been called by the national need into work which demands an approach of a qualitatively different kind from that which obtained in the consulting room or hospital. The view has frequently been voiced, and voiced with conviction, or with superciliousness, that the problems of industrial medicine are well within the scope and competence of any good all-round doctor and that, therefore, the insistence of many of us on the need for special training was so much vapour.

I hope that, in the course of this paper, it may become clear that some measure of training is necessary at least in the study of toxic materials.

I will close this short introduction by laying down a fundamental principle which must always be kept in mind in work of this kind. It is this: 'You never find anything unless you know what you are looking for.'

Those who have still a recollection of the mental processes which go on when one examines a slide of pathological tissue for diagnosis will know what is meant. What happens, roughly speaking, is this: first one tries to recognize the organ or tissue and this is done partly by experienced visual memory and partly by analysis; when this is satisfactorily concluded upon, one then tries to establish the nature of the abnormality by fitting what is seen to visual pictures of known conditions.

The process is one of asking oneself whether such or such appearance is present. In other words, one is looking for something which is already in the mind.

A similar process is gone through in a more reflex manner when a clinical examination of a patient is made. So often an abnormality is detected without the examiner being able to produce a diagnosis, because he is unable to fit his observation to an already known fact, usually a fact of pathology. This sort of thing is particularly evident in examining workers who are engaged in industrial hazards. To examine such subjects with the commendable hope that the disturbances in structure or function will be detected by means of the much advertised clinical sense, is to run the risk of missing most important cases. The situation is difficult enough when one knows what to look for; without such knowledge the likelihood of detecting early clinical changes is very remote. Indeed, this has been the case in the history of the investigation of most industrial hazards. The medical man has had to wait for manifestations of disease, which nobody could miss, before being in a position rightly to attribute them to the relevant agent.

Thus, as it seems to me, the necessity becomes apparent that the medical man must somehow obtain so vivid a picture of the pathological or pathological-physiological properties of the substances he has to deal with that clinical observations can almost at once be properly correlated.

Simple examples will at once suggest themselves.

Thus, if a medical officer is not acquainted with the fact that exposure to certain chlorinated hydrocarbons may lead to contraction of the field of vision, it will not in general occur to him to institute routine mapping of the fields, and hence he may miss the early manifestation of toxic changes. A similar situation arises in men exposed to carbon

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disulphide when a characteristic central scotoma may arise.

Let us consider another substance for a moment. Ethylene chlorohydrin is a simple derivative of ethyl alcohol—monochlor ethyl alcohol. Very little information on the properties of this compound exists in the literature, in fact only one proper paper. Men working on its manufacture in carefully prescribed conditions suffered no apparent harm for years. The advent of war led to a quite different situation, and soon a considerable number of toxic events occurred, including deaths. Here was an excellent example of the helplessness of the medical service; not knowing what to look for, it was not to be expected that the insidious action of this material would be detected at a reasonably early stage.

A vast amount of work has been done on benzol, both physiological and pathological. Clinical records exist of large numbers of cases. In spite of this, medical detection of early cases is still extremely difficult. The old claim that leucopenia was an early index of toxic effects is certainly not true in a sufficient number of cases to make it reliable as a diagnostic test. Abnormalities of bleeding- and clotting-times are probably late effects. The sulphate urine ratio is not sufficiently precise and requires massive absorption. Anaemia is probably a very valuable index, but again it is a somewhat late phenomenon. Here is, then, an instance of a compound on which much more research is still required before the medical supervision will have the proper thing to look for in its hands.

An instance which is topical is that of T.N.T. The determination of the precise period at which the process of liver damage begins is still not possible. The cry for liver function tests has been going on for many years. The precise liver function to be tested out of the innumerable things the liver can do is not known. Studies are in progress. When the crucial index of liver damage is in our hands we shall know what to look for, and perhaps eliminate the incidence of this occupational disease in its fatal forms.

A notable instance comes to my mind, which was investigated most ably by Dr. Donald Hunter and his colleagues. Here the ignorance of the manufacturers was responsible for dire events. The substance to be manufactured was methyl mercury nitrate ($\text{CH}_3\text{Hg.NO}_3$). The sequence of events is worth mentioning.

Methyl iodide (a most dangerous compound) was prepared from CH_3OH , P and iodine. This was then allowed to react with Hg under electric lamps, methyl mercuric iodide being formed. The material was broken up by tapping on rubber sheets. This was done in a room 16 feet square, with 4 skylights, 2 windows and a large double door—all open. In the next stage the dry methyl mercuric iodide was mixed with a solution of mercuric nitrate in a power-driven pestle and mortar mill.

The insoluble mercuric iodide was filtered off and

an almost saturated solution of methyl mercuric nitrate obtained. This was diluted and mixed with an inert powder, was then dried, ground and packed.

Masks, goggles and elbow gloves were worn: ventilation of the room—40 feet square—was good as far as windows, skylight and gaps in the wall could make it, but it was not good enough.

Twelve men were involved in the work; 8 showed mercury in the urine and 4 did not. There was no doubt that the symptoms of mercury poisoning, which developed in 4 cases, were due to inhalation of dust. With the exception of tremor, the usual symptoms of poisoning by inorganic mercury were absent. The nervous system only was affected. Severe generalized ataxia, dysarthria, gross constriction of the visual fields were present in all cases. Memory and intelligence were unaffected. The cases were difficult to handle and much re-education of movements was required.

Here we have an extremely toxic process, on which men were employed, without the employer *apparently* having any knowledge of the extreme hazard of the product. Hunter's investigations showed that animals exposed to the vapour of the material developed marked lesions in the brain and cord. There was even less excuse than might have been advanced on the ground that the toxic properties of methyl mercury nitrate had not been published, for the toxicity of methyl iodide is very well known.

Another example in a large chemical concern which possessed a considerable medical service is worth a note.

The process involved was the manufacture and distillation of a chlorinated aromatic amine. The compound was of great importance, and it was thought necessary to prepare the base as opposed to the hydrochloride

The operation was undertaken in a hot August. Ventilation was poor and the properties of the material had not been studied from a physiological point of view. In a very short time several of the men had developed an acute haemorrhagic cystitis. I have made a careful study of the compound involved and, as a result, it has been possible to show from purely physiological experiment that, by modifying the molecule, these effects could be prevented. By adapting the process to the modified molecular structure, it has been possible to manufacture the material required during several years without any adverse effects on the men.

One final example of ignorance leading to severe toxic results; this time on the part of a worker who, ignoring works instructions, became severely ill, unfortunately an all too common event in chemical factories. Working with a liquid—o-toluidine—the worker spilled a cubic centimetre or two into his top-boots. Instruction was that in such a case the worker should immediately report, have himself stripped, bathed and await orders. This man ignored all this. A few hours later he felt sick, and on then belatedly reporting he was found to be severely cyanosed. On return home he was later

taken with an acute haemorrhagic cystitis which his doctor was at a loss to understand. He wisely contacted my department, and it was possible for us to deal with the situation, but it took several weeks to get the patient quite better. There have been no sequelae after two years. We mention this case to show that workers must realize the character of hazards as well as managers and doctors.

I hope it will be clear from these examples that some radical attack on the problems of toxic hazards is urgent.

As the years have passed since the institution of a Factory Medical Inspectorate, a great deal of information has been accumulated by the Inspectors on the properties of many materials, but this knowledge has, in the main, been obtained from clinical cases of actual poisoning. Valuable as this has certainly been, we have no excuse nowadays, or at any rate in peace-time, for allowing cases of poisoning to occur if the physiological properties of chemical products can be determined by experiment.

Modern emphasis is on prevention, and I know of no field in industry in which this is more needed and in which more success can be attained.

I proceed, therefore, to certain aspects of the

investigation of toxic hazards. These will be elementary, but if pursued will amply repay effort.

There are four ways of discovering the physiological properties of toxic or suspected materials: (a) Literature search; (b) Physical and chemical properties; (c) Experimental study; (d) Clinical investigation.

(a) *Literature Search.* This is obvious, but not all manufacturers have installed adequate facilities for such a search. Nor is such a search to be regarded as something easy. Language facility is essential. Membership of proper libraries is needed.

In addition, a proper filing system for permanent record is required, and additions must be made as knowledge increases.

In the chemical industry, particularly the organic, the choice of such a filing system is no easy matter, but in other industries it is perhaps easier. From the doctor's point of view, he must be in a position to use his accumulated record in such a way that he can quickly and confidently transmit to the operating departments what he knows about the compounds involved.

An example of such a report form is here shown.

TOXICOLOGICAL REPORT							Ref. Date
Names of Material.							
Chemical				Formula or Composition			
Trade							
A. Physical and Chemical Data. Solid Liquid Gas Dust	Colour	Odour	M.P.	B.P.	V.P.		
	Reaction	Volatility		Particle size			
	Specific Gravity	Detection					
	Solubilities						
B. Routes of Absorption. Modes of Excretion.							
C. Known effects on man.							
	Central Nervous System and Special Senses	Respiratory	Cardio-Vascular	Gastro-Intestinal	Urinary	Other Systems	
Acute							
Chronic							
D. Toxicological Properties. Animals.							
Solid } L.D.50							
Liquid }							
Gas. Toxic concns. with times (p.p.m. (v/v) : mins.)							
Pathological effects.							
E. Probable effects in man in industrial conditions.							
F. Recommendations, Prevention and Safety.							
Plant							
Max. allowable concn. (gas or vapour)							
Protective appliances							
Medical Supervision							
G. Treatment of Poisoning. Contra-indications.							

FIG. 1.

By filling up such a report form, the doctor or any other person will immediately be in a position to see what is known and what is still required to be known.

It is clear that literature search alone is very often not sufficient. Text-books are rarely of great help, perhaps because there is no space to deal adequately with all subjects. The I.L.O. publication 'Occupation and Health' is often useful but badly requires bringing up to date. Published papers must in the last resort (or perhaps the first) be the source of information and the medical officer must often build up his own literature survey.

(b) The second method of understanding the nature of the physiological action of toxic or suspected materials is to find out oneself: the first requisite being a thorough appreciation of the *physical and chemical properties* of the material in question to the extent that these may influence the entry into the organism and the toxic effect on the latter.

Let us, first of all, consider what in general we want to know.

The decisive points must have relation to the manner in which, so far as can be foretold, the worker is likely to be exposed to the material in question. Thus, it might be said in almost every industrial problem of this kind that the worker is not asked to eat the stuff. But it cannot be assumed that, in fact, he won't ingest it.

We are all acquainted with the predatory activities of workers when faced with the bottle labelled 'Alcohol.' A case comes to mind in which a worker took home a quantity of sodium nitrite which he thought was salt: the result of using this in cooking was to kill the whole family. Another case was that of a man who, having an urge to shuffle off his mortal coil, took home a quantity of sodium cyanide from a works, retired to the cellar and ended his life.

Then we have the recorded cases of men who have drunk deeply of organic solvents.

Apart from voluntary ingestion of dangerous materials, we have the involuntary. This sort of event is not, in general, a very serious matter, but in certain industries it becomes a matter of first importance to forbid eating or chewing on the plant, and in a good many cases, nail-biters must be eliminated.

These points are mentioned because the determination of toxicity of substances given by mouth should not be regarded as of academic interest only.

It is clear that the nature of the material will determine in great measure the manner in which the organism is likely to meet it, and the route by which it is likely to be absorbed.

When reference is made to the 'nature of the material' under consideration, the least that this can mean is its chemical identity. Theoretically this should always be available, or at any rate determinable. In practice we know that very frequently the employer himself does not know what he is using. Products are used for a multitude of

purposes under bizarre and meaningless names, which are no clue to their compositions and which indeed may obscure them. It is the particular industrially important property which is emphasized and not the composition. Nowhere is this more blatant than in the case of solvents. Time and time again cases have been reported of toxic effects attributed to exposure to volatile solvents in which the offending substance was either not known to be present or from which it was specifically stated that certain toxic solvents were absent.

The 'nature of the material' must also include a statement of the degree of purity and the nature of the impurities, for the use of completely pure chemical individuals in technical processes is unusual. It will be appreciated that the physical properties determine the readiness with which the material can enter the organism.

A few simple examples may serve to indicate that the appreciation of physical properties is of great importance.

Metallic mercury has a high boiling point, and hence *a priori* it might be considered likely that in operations far below the boiling point the hazard to workers would be minimal. That this is not the case is known to all.

Cases of mercurial tremor among laboratory boys and physicists have occurred, whose contact with mercury was simply that arising from bench work. Mercury strewn in droplets on the surface of a laboratory bench volatilizes and is absorbed by the operators through the respiratory tract.

Again lead, which is used in industry in a multitude of forms, can be absorbed into the organism in the form of most insoluble salts or oxides. Lead chromate, oxides, sulphate, all practically insoluble in water, might be held to offer little chance of toxic effects, but we know perfectly well that inhaled as fine dust the organism is able to transform them into readily diffusible forms.

In the filling factories, the physical property possessed by both T.N.T. and tetryl of being soluble in lipoids lies behind the whole theory of poisoning by absorption through the skin. But care must be exercised here lest one overlooks the dust and fume hazard by over-concentrating on the skin absorption.

In general, liquids which are lipid solvents require careful assessment, for it is easy for the uninitiated to raise alarms where none is warranted. Thus, a perusal of the experimental results with dichloro-ethane (ethylene dichloride) might lead one to expect many industrial casualties. Actually, precaution is such that none has, as far as I know, been reported, although symptoms due to narcotic effects may occur.

The precautions laid down for the handling of trichloro-ethylene are well known to all those engaged in de-greasing machinery. This compound possesses in an outstanding degree many physical properties necessary for good anaesthetic action and, indeed, has recently found considerable favour among anaesthetists. But its virtues as an anaes-

thetic render it all the more necessary to treat it with caution. Chronic effects attributed to this solvent still await explanation, although its gross acute toxicity appears to be not serious.

In the vast field of organic compounds, there is a tendency to ignore purely physical properties, particularly when dealing with solids. I always look with suspicion at materials of low melting point and high or considerable lipoid solubility if in association with toxic radicles. These are the compounds which more or less readily penetrate the skin. In general, these compounds show little, if any, solubility in water.

The importance of careful control of temperature in certain processes is illustrated by the cases of toxic effects arising from the handling of chlorinated naphthalenes—synthetic waxes largely used in insulation work. The process is simple, the danger lies in not realizing or ignoring straightforward instruction. The wax melts at a certain range of temperatures, and it is required that the material should be kept molten, but not raised above a certain maximum range. When this is not done, the material gives off vapour and this vapour is both irritant to the skin and poisonous to the liver. 'Chloracne' cases have been described and liver atrophy and necrosis has occurred too frequently. The cold solid wax on the dipped articles leads to no troubles, but inhalation of toxic dust may follow processing of the articles. This is a good example of the significance of physical form and properties.

Difficulties which may be met with as to workable temperatures or as to the evolution of fume at prescribed temperatures should not be taken with indifference. Satisfaction must be demanded or the process stopped.

I think it was in a shed where this sort of process was going on that a certain medical officer, who deserves great commendation, decided that conditions were dangerous. Receiving no satisfaction from his management, he printed a notice—*This Plant is Dangerous*, affixed it to the door and cleared all the workers out.

One final example of the importance of temperature. In the rubber industry, it is often necessary to incorporate a compound which when heated liberates an inert gas. This gas enmeshed in the rubber mass creates the condition of *sponging*. The final product when cold has no irritant properties and is handled daily with impunity. But when it is hot or warm, application to the skin leads to severe dermatitis and absorption through the skin may take place and lead to cyanosis.

Another physical property of great importance is *density*, especially when dealing with a gas or vapour. In war-time plant which may have been erected in a hurry, the result may sometimes be that units of plant are rather crammed together and ventilation is unable to cope with local pockets of air. Gases or vapours greater in density than air tend to collect in such pockets. It then becomes necessary to introduce local draught, but evidence will always be sought by managements as to any higher concen-

tration at these points than in the general air space in the shed; and the doctor is well advised not to start talking before he has the data in his hands.

I have considered it desirable to multiply examples because I am by no means convinced that medical officers as yet realize the need for inquiring most meticulously into the physical properties of materials before examining the more medical aspects of toxic materials.

The *chemical properties* of industrial materials are of importance to us, in so far as they may influence the views of medical officers and the kind of advice which they will be led to give to the managements.

I take it that a safe, rough definition of a chemical property is that it is a power latent in an element or compound which permits it, in suitable conditions, to interact with other elements or compounds in a way which results in a change in the interacting materials other than change of state or aggregation.

From the point of view of the industrial toxicologist, it is evident that merely to apprehend the chemical properties of the interacting materials may be quite insufficient. He must recognize that the products of the interaction or the by-products may constitute the important feature for the investigator of hazards.

Thus, in the manufacture of certain complex dyestuffs of the sulphur colour class the initial materials used, whilst not entirely without toxic properties, are relatively easily handled with safety. But as a result of the reaction H_2S is liberated and constitutes the principal hazard.

Similarly, one may have residual materials after a reaction is completed which are potentially or actually dangerous products.

Of a potential hazard I shall give one notable example. In a process where the residual fluids contained inorganic sulphides, the run-off was into a sort of gutter. This gutter was also used by another unit for running off waste acid, but an arrangement had been made whereby the two run-offs were never run together or before water or alkali had cleared all remnants of the last run-off away. On one unfortunate occasion a misunderstanding arose and the acid met the sulphide. The result was a tremendous evolution of H_2S and a worker—a woman—collapsed and was trapped in an inaccessible spot. After extrication with great difficulty she was brought round sufficiently, in the ambulance room, to permit of her transfer to hospital. Here she had respiratory symptoms and great restlessness, both common in H_2S poisoning, and unfortunately she died within a few hours.

Now it cannot be expected by industry that the medical officer should be a chemist, but it is perfectly justifiable to expect him to know in detail the various stages of the processes and to be in a position to ask the questions which are relevant to his understanding of the hazards.

One aspect of this question of chemical properties deserves special mention. It is so often the case that information is required at short notice on the

hazards of a material that the medical man, failing relevant literature, may have to make a guess. Although it is always possible to make a guess on the safe side, one looks a little foolish if later information reveals that his guessed apprehensions were so much warmed air. We call this sort of guess toxicity by analogy, but in order to do it in the organic field with some degree of verisimilitude it is necessary to comprehend the significance of structural formulae.

The correlation of chemical structure with pharmacological or toxic action has never been attained except in isolated cases. I think we should all agree that there is no obvious reason for quinine to be so potent against the plasmodium or for Bayer 205 against the trypanosome. Some advance is being made on the lines of the action of sulphonamide in competing for p-aminobenzoic acid against the demands of the haemolytic streptococcus.

But in general, in the field of toxicology, we must rely on *ab initio* investigation or on experience, taking into account all the physical and chemical properties which appear relevant.

The specificity of toxic effects in relation to chemical structure is sometimes striking. This is a vast subject in itself, but I will choose two examples.

The following three substances are isomeric:

The first of these produces in certain circumstances rapid and violent haemorrhagic cystitis, both experimentally and clinically; the others do not.

The following two compounds are also isomeric:

All are familiar with the depressor activity of nitrites, but the nitro-paraffins do not act in a similar way.

Guessing in cases such as these is dangerous.

But from our knowledge that

we can reasonably offer the guess that

The important chemical properties of *reduction* and *oxidation* should always be kept in mind.

Whereas the organism has mechanisms for buffering extraordinarily large amounts of acid and alkali, it is less endowed for dealing with reducing and oxidizing compounds. It is true that considerable concentrations of reducing agents exist in the blood, but these are not in a position to exert this property because the reaction conditions are not suitable.

The absorption into the circulation of oxidizing and reducing agents, which can exert these properties at the reaction of blood, will exert profound effects on the blood pigment and lead to all the consequences of interference with the oxygen-carrying capacity of haemoglobin.

Powerful oxidizing and reducing agents exert a deleterious action on the skin, a fact which should always influence the medical officer in criticizing the well-known agents used for skin cleansing.

On the importance of the *acidity* or *alkalinity* of compounds in aqueous solution all will be informed, but special mention must be made of two materials which require the utmost attention at all times: *ammonia* and *lime*. These compounds have most devastating effects if they enter the eye. Ammonia liquid in the eye, after what has appeared to be adequate irrigation and relief of symptoms, can continue to exert a steady effect leading to clouding of the cornea, penetration into the anterior chamber and disintegration of the lens.

In the case of lime it is usual to attempt neutralization of the caustic effect by irrigation with ammonium chloride or tartrate. Some ammonia is formed, but is soon swept away and the calcium is solubilized. The occurrence of such cases indicates lax safety supervision. Quicklime must never be handled without goggles. The lime burn in the eye often leads to an angry, resistant granular conjunctivitis, with a tendency to burrow under the bulb and may produce a permanent ectropion.

In both these cases the utmost speed of action is essential so that appropriate apparatus is required wherever the hazards exist.

In considering the chemical properties of a material, it is well to keep in mind its possible action on some essential constituent in the organism. A simple example is, say, oxalic acid. Apart from being an irritant poison it kills by removing ionized calcium from the blood, if absorbed.

Similarly the relation of fluorine and hydrofluoric acid to calcium will come to mind as also the use of injection locally of calcium gluconate in cases of hydrofluoric acid burns. The relevance of remembering decomposition products of compounds is shown in the case of phosgene, the effect of which is almost certainly related to the liberation of active HCl.

The use of oxygen and of oxygen-carbon dioxide mixtures is known to all as perhaps our most valuable stimuli to the cardiac and respiratory systems, but in some cases the value of oxygen is based upon the chemical properties of the toxic material which

led to its use. Carbon monoxide springs to the mind. Here by increasing the oxygen tension in the blood the reaction $\text{Hb} + \text{CO} \rightarrow \text{Hb.CO}$ is more readily reversed and the CO removed.

Let us examine the case of methaemoglobinaemia. Here the iron in some of the blood pigment is in the oxidized ferric state and cannot carry oxygen. The use of O_2 or $\text{O}_2\text{—CO}_2$ is here dictated by the need to assure a maximum saturation of such haemoglobin as is still functional until such time as a more normal concentration of Hb is reached. The use in such cases of intravenous methylene blue is based upon its property of being a powerful hydrogen acceptor. Thus, in the tissues a favourable condition is produced for the liberation of intramolecular oxygen for the support of tissues deprived of normal oxygen supply by the abnormal state of the blood pigment. The application of methylene blue in cyanide poisoning has the same background since cyanide inhibits tissue oxidation.

The property of protein precipitation possessed by such agents as tannic acid, tri-chloroacetic acid, picric acid, etc., lies behind their use as agents in the treatment of burns.

The deposition of lead in the bony skeleton depends on the possibility of a double decomposition of calcium phosphates and lead compounds.

The formation of the silicotic nodule possibly depends upon the slow formation of silicic acid at points of deposition of silica particles.

These are all elementary points serving to show that a proper assessment of chemical properties is necessary to the medical officer who aims to visualize his hazards as they act and to understand the rationale of his therapeutic measures.

(c) *Experimental Studies.* With all the efforts the doctor may make to establish the toxic properties of his materials, the time must come when he is faced with substances about which little or nothing is known from the toxicological point of view or about which he feels that extant information is unsatisfactory.

In such event, apart from the precarious guess method, he has no alternative except *experimental* and/or *clinical investigation*.

Experimental investigation involves laboratory studies on *animals*.

Now it is customary to cast a somewhat dubious eye at animal work in this and other fields and, indeed, one may perhaps ascribe to this attitude the rapid disappearance of animal experiment or demonstration after the second year or so of medical studies. This is a pity, for it is by animal experiment that we can develop a grasp of process as opposed to established change in tissues. The object of medical investigation is far more to obtain knowledge on the process of attack on and change in the cell than merely to describe the terminal state in which the cell finds itself. The need for this state of mind will be at once apparent in such a field as cancer investigation. Of course, the appropriate techniques have to be developed and therein most often lie the difficulties.

Animal experiment can give a great deal of information, but its application to the human subject requires considerable care and experience. The quantitative aspect can be fairly accurate in animal work, but indiscriminate acceptance of animal figures for human subjects would be, in many cases, unjustified.

We have further to remember that, if it were possible to carry out experiments on men, we should still be faced with the factor of *individual variation* which would prevent a universal application of results to all subjects. We all know of cases that can take aspirin or quinine and others who cannot. Similarly we have individual variation to skin hazards and even gases. And this individual variation is not, in general, referable to manifest structural signs. An apparently completely uniform population of animals shows marked individual variations even in the most carefully controlled conditions. The term *toxic dose* of any material thus requires careful consideration, for whilst a given dose may be toxic or lethal to a certain proportion of a given group of animals of a particular species, it will not necessarily be so to all.

We reserve for a later contribution the consideration of aspects of the experimental determination of toxicity and the interpretation to be applied in industrial problems.

Reference has been made to individual variation within any given species, but variation as between species may be even greater. Hence the application of such findings to man is always a matter only of suggestive inference. In pharmacological studies determination of M.L.D. (i.e. median lethal dose = dose which in the long run will kill 50 per cent. of animals) is always a necessary preliminary to utilization of drugs in human subjects. But one has to be prepared for adverse findings in man. A topical example will perhaps be of interest.

In research to develop new compounds of the sulphonamide type, a compound was prepared which, as far as animals were concerned, possessed admirably the properties required: it had powerful bacteriostatic activity, a low toxicity, did not produce cyanosis and so on. But on application in the ward in therapeutic doses, the degree of cyanosis produced in man was so great that the substance had to be abandoned. Clearly there was some difference between the power to detoxicate this compound in the rodent and in man.

An industrial hazard with which wrong conclusions might have been drawn is aniline. If the toxicity of this amine had first been studied in the rabbit, a quite false conclusion would have been reached. For whereas aniline produces severe and even fatal cyanosis in man, I have never been able to obtain cyanosis in the rabbit. On the other hand, the rat or mouse or cat or dog would have put one on the right path.

Let us take an example where the sensitivity of the animal is so great that its reaction is used as a most valuable index of impending danger. The case of carbon monoxide is outstanding. Mice

exposed to a concentration of some 500 parts per million ($\frac{v}{v}$) for 20 minutes will react with unmistakable toxic effects, whereas men can support this concentration for at least an hour without trouble. But one does not risk this. If the mouse shows symptoms, the working place is cleared.

But the mouse or canary are by no means infallible in detecting hazardous concentrations of all toxic gases.

These are simple examples. Much greater difficulties of decision are the daily lot of the doctor in the chemical industry.

An example: For certain complicated processes cyanuric chloride (CNCl_3)—a solid—must be used. Now the toxicity of this material is very high—5 mg./kg. for mice when injected or given by mouth—and one becomes anxious. But the circumstances in which the compound appears in the processes render it most unlikely to be absorbed by the worker. On the other hand, a compound like crotonaldehyde cyanhydrin—a liquid with a pungent vapour—cannot be used without some degree of transference into different vessels with escape of vapour, and hence its very high toxicity, easily demonstrable on animals, renders it a hazard of great importance.

Thus toxicity in the industrial sense *must have relation to the circumstances of manufacture or use*. Hence the significance of the doctor's knowledge of plant and process. It is this aspect of industrial medicine on which so much emphasis must be laid if its value to industry is to be established.

The intimate knowledge of plant required by the doctor if he is to pronounce with confidence is such that it becomes necessary for him actually to work in the shed with the worker. This is realized in some American factories where the young, or even not so young, doctor spends several months actually as a worker, doing day and shift work and thus learning not only the nature of chemical plant and process but also the worker's terminology.

Every industry has its own 'argot' and the doctor should know it.

Moreover, the experienced worker has a knowledge which, if properly tapped, will open the eyes of the doctor to many things not to be found either in text-books or in the literature. Toxicity data in application must have relation to the *habits of workers*. It must always be kept in mind that the factory life of a worker becomes after some time a psychological and physical conditioning to external requirements. The result is a more or less uniform pattern of behaviour, and this must be apprehended and understood by the doctor. Recommendations based entirely on laboratory findings as to toxicity without regard to such patterns of workers' behaviour are of little practical value. For, to implement recommendations designed to prevent toxic events requires the understanding collaboration of the worker. If all processes could be carried out in totally enclosed plant, such collaboration might be unnecessary, but such an ideal is never likely to be attained except in a minority of processes.

An example is worth quoting.

You will all know that satisfactory germination in 100 per cent. of seeds is not possible in most soils unless measures are taken to protect the seed against certain fungi. Among such protective agents is a group of organic mercurial compounds. The early experience in the manufacture of one of these was such that it became clear that only if total enclosure were practised could reasonable security of the workers be assured. This compound attacks the skin with production of a bullous dermatitis. In the present process, there is absolute enclosure from the time of mixture of the primary reactants until the automatic delivery of the final product into the receiving tins. So satisfactory is now the process of manufacture that cases are not met on the plant, but practically only in the dressing of the seed by the seed-dresser and in the sowing by the farmer. Proper precaution by the former should in general obviate trouble and, in the latter case, it is only in cases of exceptional sensitivity that trouble arises.

This is the more striking when we consider that the seed is dressed with a diluted product containing only from 1 to 1.5 per cent. of calculated Hg.

I recently saw some cases of distressing character in a farming area, which are worth mentioning. A young farmer had developed an erythematous-vesicular rash as a result of handling dressed seed without proper precaution; he visited his doctor who diagnosed scabies as the condition was certainly very itchy. The patient was plunged into hot baths and scrubbed and inuncted with sulphur ointment. The result was a fearsome mess. When I saw the case, it was one of a generalized, oozing sulphur dermatitis, chronic and intractable.

The fault here lay partly with the farmer, mainly with the doctor, but also in part with the manufacturer who had not sufficiently disseminated knowledge on this particular hazard. Properly treated, the condition can be completely cured even in severe cases in less than three weeks or a month.

But the intelligent co-operation of the worker is essential both in prevention and in treatment.

The example just quoted—it was one of three of varying severity—illustrates another aspect of the responsibility of the doctor engaged in the chemical industry, viz. *responsibility to the user of chemical products*. He must not only prescribe for the protection of his workers in the factory where the product is manufactured, but also be prepared to inform users of its actual or potential dangers and how best to circumvent or neutralize them. No amount of academic knowledge will overcome the problems involved. Such knowledge must be combined with an appreciation of working conditions and the circumstances of exposure. Untoward events may occur which demand an immediate response from the medical officer as to the hazards of the products of his industry. Two mild examples in the dyestuffs industry are of interest.

The first was a trivial event, but led to great anxiety. A child in a Midland town was left alone

at home and proceeded to eat a tablet or bag of the housewife's material known as Dolly Blue or some such name. I surmise that the child looked a pretty sight when mother returned. The alarm was rung, but the dyestuff involved is very soluble and rapidly excreted. Simple diuretics were advised and a mild purge, and in a day or two all appeared to be well.

The second is an amusing case. A certain small dyeing concern operates in an agricultural region and was in the habit of liberating not inconsiderable effluents into a small stream at which the local cows could drink. The principal dyestuff these people used is a black. Now a black dye may contain much beside black compounds. The local authorities raised considerable objections to this. The M.L.D. of the material was found to be so high as to be negligible, but it was clearly also necessary to find how the dye was excreted. So metabolism experiments were set up and on collecting the urine of animals treated with the dye, it was found that a red dye was excreted. Study of this dye in the urine led to its identification as one of the shading materials in the original mixture. Now whilst it could be concluded that the cows would not suffer grievous harm from taking a drink of this unattractive cock-tail, it was by no means certain that the milk would not be of a somewhat revolutionary colour if sufficient of the stuff were taken. So the practice was condemned and the firm had to make suitable alternative arrangements.

In the days when the Channel Islands were in a non-infected state, we received great quantities of tomatoes from them and certain grades of tomatoes were made into tomato puree. Now, as in the case of browned kippers, this country will not eat the product unless it is dyed a nice juicy colour. The dye used is harmless and is added in small amounts. But there must be an assurance that the colour will be maintained in the can almost indefinitely.

A very large quantity was thus prepared during a period some years ago and canned. When some time later a few cans were opened by customers who had bought them at a grocer's, they discovered with alarm that the puree was a jaundiced mess instead of a juicy red. The canners demanded a very heavy indemnity for what was going to be a total loss. Arguments of various kinds were used on both sides, and it was alleged that there was something wrong with the dye which was now probably a dangerous poison.

Now clearly there were three main factors—the dye, the tomatoes and the can.

It was easily demonstrated that the dye was the same as had always been used, the tomatoes could be assumed as the same, so the trouble must have been in the can. The can was tinned iron and it was easy to show that iron reduced the dye to a yellow derivative.

An agreement was reached, since it could still be claimed that the dyestuff makers had not informed the user as to the effects of ferrous metals on the colour.

These examples will perhaps serve to show you that there are aspects of the work of an industrial doctor engaged with toxicological matters which can exercise the mind in manners not usually associated with doctoring. It is not to be supposed that industrial doctoring in general entails work of this kind. But it is in the highest degree desirable that more people should be engaged in it as a constant guard against calamities which occur as a result of ignorance, neglect and indifference in the handling of industrial materials, many, very many, of which exert toxic effects.

The Skin

No discussion of industrial hazards can overlook reference to the skin. As an industrial route of entry of toxic products into the organism, the skin is second only to the lungs. Reference has been made to the rough general criteria of skin absorbability—viz. low melting point, lipoid solubility or miscibility, fat solvents.

But it is not only the properties of the material which determine ease of skin absorption. The condition of the skin itself is a determining factor—hot, greasy, perspiring, for example. Experience, often after notable toxic events, has taught us in the past that certain materials are absorbed through the skin, e.g. aniline, nitrobenzene, toluidine, lead tetra-ethyl, mercury, carbon disulphide, etc.

To determine of a new material whether it is likely to be absorbed in this way, the physical properties are a very useful guide. But the demonstration on the animal is always desirable, particularly if the material is toxic.

The experimental pathology of the dermatologist is only exceptionally carried out on animals. The reasons for this are obvious. But in the matter of absorption, provided a dehaired area of skin is used, reasonable conclusions can be drawn. There are technical difficulties as, e.g. prevention of licking both by the individual animals and by others, the maintenance of the part exposed without exposing to absorption by the respiratory tract, prevention of removal of material and so on.

It will be convenient to use my reference to the skin to introduce some notions on the importance of a competent knowledge of pathology—both clinical and experimental—in this kind of work.

Let us for a moment consider the place of pathology in general medicine. I think it true to say that it is the science of topographical and histological description of morbid processes. Experimental pathology attempts to relate causes to the findings of topography and histology.

Now it seems to me that, if man is to intervene successfully in the process of disease, some way must be found to eliminate causes or, if that is not attainable at any stage, to get between the cause and the establishment of the morbid changes. The implication is simply that we must not wait for post-mortem material to establish a pathology. It is, in my submission, a most depressing business to wade through the immense contributions of the German

schools of morbid anatomy and to realize how little has emerged which helps us to attack morbid process at a hopeful stage or with hopeful methods.

In the field of work under discussion, immediate causes are in greater or lesser measure determinable and, as has been pointed out, it is theoretically possible completely to eliminate industrial poisoning and disease. As long, however, as man must use his hands to work so long will we have industrial skin disease. And as long as processes cannot all be completely enclosed or otherwise made safe when toxic materials are used, so long will we have poisoning and disease in industry.

When, therefore, the doctor considers the hazards of his industry, he must be in a position to visualize what is going on in and on his workers during their exposure to the toxic materials.

To obtain this view animal experiment in the first place is a *sine qua non*, and complete physiological and pathological study a necessary preliminary to establishing the needed control over the health of the workers.

As to physiology, the effects on respiration, circulation, nerve transmission, isolated tissues, secretions, reflexes should be studied. The metabolism of the material, i.e. the changes it undergoes in the organism and the retention in the tissues, must be dealt with. In certain cases, the absorption of the material can be gauged by the degree of excretion in the urine (and faeces in some cases), and methods must be devised to determine the excreted products quantitatively. In other cases, studies must be made of the effects on the blood and blood-forming organs, on the composition of the urine, on the pigments of the blood, on the digestive processes and so on.

These things must be done both as acute and chronic experiments.

On the pathological side, sections of organs must be prepared to find changes in structure, both from minute exposure and massive exposure for short and long periods. Correlations with physiological findings have to be made so that as far as may be one can visualize what is going on and obtain an indication of the point of necessary intervention when dealing with the workman himself.

The effects of a host of materials on the skin present a most difficult problem.

Of the direct attackers of the skin little need be said; strong acids and alkalis, halogen derivatives of sulphur, organic sulphates, certain organic arsenicals, certain chlorinated hydrocarbons, etc., require little investigation relatively. It is when we come to those substances to which some people are sensitive, or which set up a sensitivity, that considerable difficulty arises in experimental study. The usual laboratory animals possess skin which is different structurally and functionally from human skin, and hence response to industrial dermatitic agents is different.

Still, it is possible in a sufficient number of cases to establish what corresponds to dermatitis on animal skin—rabbit, mouse, rat, guinea-pig, horse

and pig are probably better animals to use, but not easy to do so.

Much has been written on the patch test.

The application of this test in industry is, in my view, impracticable and in general not justifiable.

In hospital or at a skin clinic, this sort of test to determine sensitivity to a specific agent is possible, but in a factory it is a most delicate matter and if undertaken must have the written acquiescence of the worker subject—otherwise unending trouble may arise.

Taken all in all, we must rely on clues from animal work and, where these are not very satisfactory, on analogy and observation in the factory.

Since the acute reactions of human skin to industrial dermatitic agents are very similar to those in cases of eczema of which the gross pathology is known, it is possible for the medical officer to draw conclusions at a very early stage, provided the cases are made to report at the onset.

But there are many reactions to dermatitic agents other than the eczematous, e.g. acneiform, bullous, urticarial, pure oedema of a massive character, etc.

And extremely frequently there occurs simultaneously with the skin condition, or sometimes preceding it, a marked oedema of the lids and sometimes a conjunctivitis with persistent lachrymation.

(d) *Clinical Study of Industrial Hazards.* I think it will be wise to state at once that the possibility of clinical study of workers by the factory doctor was, until relatively recently, overshadowed by the business of compensation. It was natural for the workman to look askance at a doctor appointed by an employer, since it appeared to him that such an appointment could only be in the interest of the employer and hence likely to operate against the worker's interests. It is probable that in a good many instances there was justification for this view, but things have changed in recent years. As a consequence, clinical examinations to detect signs or symptoms of industrial poisoning have become easier to institute. It is difficult except in those cases where examination is required by law, e.g. for lead, phosphorus and so on. But there are many materials which demand that regular examinations should be done to detect early signs of disease which are not formally scheduled under Act of Parliament. And, further, it has got to be remembered that to examine a man's blood or urine, say once a month, is a procedure which produces considerable anxiety in his mind and perhaps even more in the mind of his wife.

Explanation by the doctor of the need for repeated examination is likely to produce quite wrong conceptions in a man's mind and even if right ideas are implanted the reaction will often be—'If the stuff is dangerous I want more money': this may be a justifiable position to take up, but since more money will not help the doctor in his control of the hazard, it is not of much value from the present point of view.

It will thus be seen that much tact and understanding of the worker is called for. In order not

to produce a scare in a particular department or plant, it is essential very often to spread the examinations over a number of sections and thus, willy nilly, one collects control data.

The psychological situation as between a doctor and patient who consults him is quite different from that between an industrial doctor and a worker who feels quite well and has not consulted him. Where objective observations can be made, it is relatively uncomplicated, but so much depends on the accurate presentation of subjective symptoms, which the workman may be and often is disinclined to divulge if they appear minor.

A plant was recently inspected where many of the workers quietly left the shed, went round the back and had a quiet and private vomit several times a week and never volunteered the information or even made complaint. Many other instances in various trades could be given.

It has always to be kept in mind that very few substances limit their action to single organs or systems, e.g.—

General Systemic Poisoning. Pb, As, CH_3OH , CS_2 .

Circulatory Poisons. $\text{C}_6\text{H}_5\text{NH}_2$, As, $\text{C}_6\text{H}_4(\text{NO}_2)_2$, Pb, Hg, Va, C_6H_6 , T.N.T., $\text{C}_6\text{H}_5\text{NO}_2$, CO.

Respiratory Poisons. Si, NH_3 , nitrogen oxides, Cl, SO_2 , H_2S , cobalt arsenide.

Gastro-Intestinal Poisons. Zn, Pb, As, Hg, Cd, Sb, C_6H_6 , cyanide, nitro and amido bodies, tetrachlorethane.

Dermatitic Agents. X-rays, actinic rays, HCHO , tar, benzene, cutting oils, ZnCl_2 , hexamine, p-phenylene diamine, chromates, petroleum oils, etc.

Action on Skeleton and Joints. Pb, P, acids, As, Hg, mesothorium.

Action on Organs of Special Sense. CH_3OH , actinic rays, intense light, Pb, As, HCN, H_2S , CS_2 , Hg, turpentine, Mn, C_6H_6 .

Action on Genito-Urinary System. Aniline, benzene, Pb, As, Hg, x-ray, Va, turpentine, b-naphthylamine, phenol, nitroglycerine, ether, p-nitro-aniline.

Action on Brain and Nervous System. Pb, Mn, As, CS_2 , ether, phenol, cyanide, CH_3OH , trichloroethylene, nitroglycerine, some chlorinated hydrocarbons.

The organization and systematic record of examination of workers are no easy matters and require the most careful study in every case.

Record cards are also required for routine examinations of units of plant: the use of such cards depends entirely on the doctor knowing where and how to look for trouble.