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Industrial Toxicology

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THE object of industrial toxicology is to obtain knowledge of the possible dangerous effects of industrial materials before they are made or used, and thereby to be forewarned as to the nature and degree of precaution, protection and supervision which are called for if the health of workpeople is not to be affected.

This is the pure meaning of our subject. In an extended meaning it includes also the toxicology of materials in the interest of those who, neither making nor using them in industry, may yet consume them, use them in the home, come into close contact with them in apparel, use them in their hobbies, use them as a weapon against pests of many kinds, and in other ways demand protection or foreknowledge. On this occasion I am concerned with industrial toxicology in the pure sense.

The assumption is that industrial toxicology has a scientific basis. Inasmuch as it engages chemists, physicists, physiologists, pathologists, and medical men, it may claim to have science in its body in greater or less measure.

The pursuit of industrial toxicology is, as I have said on another occasion, 'not a question of Industrial Policy, but one of science, of conscience and of civility'. We may recall some notable words uttered by Einstein in 1938:

> It is not enough that you should understand about applied science in order that your work may increase man's blessings. Concern for man and his fate must always form the chief interest of all technical endeavours, concern for the great unsolved problems of the organization of labour and the distribution of goods—in order that the

creations of our mind shall be a blessing and not a curse to mankind. Never forget this in the midst of your diagrams and equations.

This quotation contains the crux of the aim of industrial toxicology, since it is first and above all concerned that the creations of the ingenuity of men although, in the issue, directed to be a blessing, shall not at any stage be a curse to men at however humble a level.

What kind of science is it, then, which embraces such diverse activities as those of the persons directly engaged in it? We may here quote a useful definition of science given by Conant (1951): 'Science is an interconnected series of concepts and conceptual schemes that have developed as a result of experimentation and observation and are fruitful of further experimentation and observation.' A great encouragement to the young, and a chastener to the conservative not so young.

The two processes of experiment and observation embrace everything that takes place in industrial toxicology, but in a sense somewhat different from that implied in the definition. For, whereas in the definition observation is a process which follows upon controlled experiment, in our science there is also observation which follows upon uncontrolled experiment. Inasmuch as uncontrolled experiment is not truly science, our science is a combination of something which is not science and something which is.

Industrial toxicology is an activity which, in all its aspects, whether clinical or experimental, whether theoretical or practical, is directed toward the frustration of thoughtless people and noxious things. The frustration of thoughtless people, workers or employers, is the more difficult by far.

Uncontrolled Experiment

When a workman is placed in a particular kind of work, a kind of uncontrolled experiment is being started. Except in rare situations there is little or no knowledge of how the man will respond physically or psychologically to the work and to the environment in which he will be required to spend one-third or more of his life.

The concept *man* is a variable; the work may be a constant, but the environment is rarely controlled, and except in those minima laid down by law, most rarely measured. From these facts many of the dilemmas of industrial medicine arise. In our field the environment may be measured in respect of contaminants (dusts, fumes, gases, vapours), and may even, in the issue, be controlled by appropriate measures, but the criteria whereby a judgement can be made that one or more workers are being adversely affected rest upon a mixture of the clinical art and clinical science.

The variability of response and interpretation in the cases of different human subjects rests in part upon:

1. the varying tolerance and detoxicating powers;

2. the variable symptoms and objective signs for a given toxic agent;

3. the variable subjective responses to signs and symptoms;

4. the difficulty in measuring significance of small deflections from the normal;

5. the difficulty of measuring *exposure* in anything like absolute terms;

6. the fears of many workpeople that complaint or confirmed symptoms may prejudice their job;

7. the fear of the employer that he may be subjected to criticism or penalty;

8. the not infrequent difficulty of attribution when many substances are involved, and

9. the identity of a symptom-and-sign-complex with others known to occur in the non-industrial population.

By no stretch of the imagination could an activity involving these and kindred factors be called a science. It may be that a scientist could pursue some aspects of it with more success than others with less training, but it is fair to say that the gift of interpretation often resides in men and women who would scarcely claim to be scientific.

But, unlike the clinician, medical observers in the field possess certain advantages which mitigate the usual charges against purely observational medicine. By constant or nearly constant contact with persons exposed to industrial materials, the frequent *post hoc* fallacy [illegible] avoided. Secondly, from the very existence of numerous people thus exposed, the range of observation more nearly approaches that of the experimental method. Thirdly, intuition and authoritarian experience are less called upon in industry than by the clinical observer—objective demonstration is more frequently attainable.

Nevertheless, it remains certain that for the individual worker as a patient the need for clinical intuition and experience remains, especially in the diagnosis of industrial as against non-industrial conditions.

Writing of the diagnosis of fatigue (one of the most difficult of all things to evaluate in industry) Patrici of Modena says: 'The symptoms are not bound together like links in a chain so that the failure of one link breaks the chain, but rather like the thousands of fine strands of an electric wire, the rupture of which still permits the lamp to glow and the experienced man still sees clearly', and this dictum may well be applied to the diagnosis of many industrial maladies.

Notifiable and Prescribed Industrial Diseases

The law in this country lays down two sets of industrial poisonings known respectively as notifiable industrial diseases (to which one may conveniently add gassing accidents) and prescribed industrial diseases. The Ministry of Labour and National Service is the responsible Government department in the former case; the Ministry of Pensions administers the provisions of the Industrial Injuries Act relative to the latter.

These lists have been drawn up from data *derived exclusively from human cases* of poisoning and disease occurring in industry and attributed to specific substances in most cases. Almost all the notifiable diseases are included in the much larger list of prescribed diseases. The words *accident* and *disease* have been the subjects of much discussion, but it will perhaps be sufficient to say that they are distinguishable by the fact that an industrial accident is not foreseen whereas an industrial disease is foreseeable once it is agreed that it can arise in more or less defined circumstances.

In no case, as far as we know, has a disease been put into these lists as a result of experimental effects with particular

TABLE 1. Notifiable diseases (Section 66 of the Factories Act, 1937)

Pb, P, As, Hg, Anthrax, CS_2, Aniline, Chrome, Benzene, Mn
Toxic jaundice (tetrachloroethane, nitro or amino derivatives of benzene or its homologues)
Epitheliomatous ulceration (pitch, tar, bitumen, mineral oil, paraffin, or any product or residue of them)
Chrome ulceration (chromic acid, $K_2Cr_2O_7$, Na_2 or $(NH_4)_2$, or preparation of)
Compressed-air illness
Toxic anaemia

Gassing Accidents

CO	Cl	Naphtha	$COCl_2$
CO_2	Nitrous fume	Petrol and benzine	HCl
H_2S	NH_3	Trichloroethylene	HCN
SO_2	C_2H_2	Nickel carbonyl	Bitumen, tar, creosote, oil
			Others
Total:	1953: 254 (23 fatal)		1954: 237 (21 fatal)
	CO, 1953: 121 (19 fatal)		CO, 1954: 113 (14 fatal)

TABLE 2. Prescribed diseases (causes or nature of)

Pb	Dioxan	X-rays, ionizing particles, Ra, etc., or other forms of radiant energy	Skin, subcutaneous tissues, bones, leukaemia, aplastic anaemia, etc.
Mn	Methyl bromide	Infra-red radiation or glare from molten glass or molten red-hot metal	Cataract
P	Chlorinated naphthalene	Compressed-air illness	
As	Nickel carbonyl	Telegraphists' cramp	
Hg	Nitrous fume	Wireless cramp	
CS_2	Gonioma kamassi	Twisters' cramp	
Be	Anthrax	Subcutaneous cellulitis (beat hand)	
Ni process	Glanders	Beat knee and elbow	
α-, β-naphthylamine (auramine, magenta)	Leptospira icterohaemorrhagica	Synovitis	
Benzene or homologues	Ankylostomiasis	Miners' nystagmus	
Nitro or amino derivatives of benzene or homologues		Tuberculosis—nurses and research	
Dinitrophenol or homologues		Pneumoconioses	
Tetrachlorethane		Byssinosis	
Triphenyl, Tricresyl phosphates			

Tar, pitch, bitumen, mineral oil, paraffin, soot or compound or residue: (*a*) Corneal ulceration; (*b*) Skin papilloma; (*c*) Epithelioma of skin

Chrome: (*a*) Ulceration due to chrome compounds.
(*b*) Nasal, upper respiratory passages, mouth, ulceration due to dust, liquid or vapour.

substances. Laboratory evidence that a material or a process is dangerous is of no moment as far as notification or prescription is concerned unless workers have been demonstrably affected by them. Laboratory evidence may fortify a contention, but in itself is unacceptable as a means of defining a notifiable or industrial disease.

Experimental evidence obtained in animal experiment is so often different from that obtained from observation of human subjects that it is rarely adduced even in a claim of damage against an employer. This latter fact is also in part due to the common attitude toward animal experimentation and to the judicial profundity which may observe that neither a rat nor a dog is a man.

Now the object of compulsory *notification* is to maintain an effective watch on what is going on in industry in respect of certain compounds.

Gassing accidents are reportable under accidents—an accident being defined as not an accident if there is not a loss of three days' working time. As to gases or vapours which do not appear as causes of notifiable diseases, it may be concluded that it is held officially that they do not give rise to disease. That is, that repeated absorption at subclinical levels of the material in question does not lead to a foreseeable disease. For example, CO and most chlorinated hydrocarbon solvents may give rise to gassing accidents but are not admitted as causes of notifiable disease or prescribable disease. Only tetrachlorethane is included in the notifiable list. On the other hand, aniline poisoning is included as a cause of notifiable disease, but must be held to cover much more than aniline. The presumed *disease* would include: anaemia, haematuria, dysuria, frequency, methaemoglobinaemia. There is no doubt that severe cases of absorption of aniline or its homologues can lead to acute haemorrhagic cystitis which is sometimes severe but responds to treatment.

Notification is rendered powerful by the duty of notification having been laid not only on the medical practitioner who sees the case, but also on the employer. As a true research tool it could give the most complete picture of every kind of industrial toxic event if its scope were enlarged. It is highly probable that as it is this country may with justice claim its records to be the most complete in the world.

Nevertheless, the Chief Inspector of Factories has indicated in at least one industrial disease that notification is incomplete. He stated in his report for 1953:

> It is evident that the notifications in compliance with Section 66 of the Factories Act, 1937, are only a partial indication of the incidence of this disease [Epitheliomatous Ulceration due to Pitch, Tar and Mineral Oils.] The duties of the medical practitioner and of the employer as regards notification are of prime importance for prevention, since the application of preventive measures to new processes and their intensification *in recognized hazards* are the immediate sequelae.

Having regard to the manifold difficulties already referred to, it is no criticism of the law or the Factory Department to say that we do not consider the figures presented in the annual reports of the chief inspector as giving a *full* picture of what is happening.

Some two years ago I made the following statement at a Conference of the Occupational Hygiene Society (Goldblatt, 1954): '. . . people who are absent for three days or more are notified, but how many people are from day to day absorbing compounds of greater or less toxic powers, without anybody knowing what ultimate effects they may have, or indeed, what immediate effects they are having?'

At the same conference, I referred to workers having been found in factories who were without doubt suffering from chronic plumbism and had never been notified at all, and in my Mackenzie Lecture of 1954 made reference also to the excellent observations of Dr. Mary Fullerton on such cases (Goldblatt, 1955; Fullerton, 1952). It is therefore interesting to note the remarks of H.M. Inspector of Factories, R. Murray (1955): '. . . there is no doubt that the data available at present are inadequate to assess fully the true incidence of industrial disease and to recognize the part played by working conditions in the causation of disease.'

Field Work in Industrial Toxicology

The work done in this context by industrial doctors, appointed factory doctors and the very highly skilled members of the Factory Department, *is industrial toxicology in its most difficult aspect.* That it is not science as ordinarily understood is rather praise than blame.

Inevitably the methods of clinical science are enlisted to fortify a diagnosis (blood, urine, X-ray, E.C.G., blood pressure, eyes, etc.), but in the issue it is the nature and degree of loss of faculty which must be concluded upon, and the strongest evidence derives from the clinical art and the occupational history.

The frequent absence of the toxic agent from the body fluids is no evidence against its having been the cause; e.g., recognizable occupational cancer may be first established long after all vestige of the agent has disappeared; the inability to demonstrate chemically the presence on the skin of any agent which might have caused a dermatitis leads to the need for indirect evidence of its culpability; in respiratory disease induced by the chronic inhalation of certain metallic oxides it may be impossible to show the presence of the metal in the body; irreversible effects on the kidneys and the circulation of a former lead worker may be attributed to that metal long after the blood, urine or tissue levels are indistinguishable from normal; the attribution of a blood disease to benzene in most cases rests on no chemical confirmation.

The experimental demonstration of the length of time a material or its metabolites may be retained in the body invokes the use of labelled compounds. Thus, working with my colleagues Henson and Somerville and using $2\text{-}[8\text{-}^{14}C]$naphthylamine, it was possible to show that radioactivity was detectable in rats and rabbits for some nine to ten weeks after a single intraperitoneal injection of 1 mg. (i.e. 5 mg./kg. for rats and 0·5 mg./kg. for rabbits (Henson *et al.*, 1954).

The significance of such findings when considering cumulation is manifest. Workmen may replenish the remnants of a day's absorption by the absorption of the following day and thus maintain residues for years in their blood or tissues. The mobilization of such residues varies with the individual, with the material, with the nutrition and fluid balance. In a considerable number of deaths reported recently among Dyaks engaged in the treatment of wood with pentachlorophenol there was without doubt a build-up of this compound by per cutem absorption, low state of nutrition and probably a poor water-balance.

The enormous fund of data on clinical signs and symptoms combined with the records of pathological changes in the organs and fluids constitutes the background from which the results of exposure to known hazard can be recognized. Where, however, no certainty as to the effects of new materials is extant, their recognition rests upon the clinical acumen of the men in the field. That this recognition can be greatly facilitated by the results of laboratory experiment is part of the case for scientific industrial toxicology.

The Industrial Doctor in the Factory

There is little doubt in my mind after over twenty years in the field that industrial doctors are regarded with dubiety by their medical colleagues in what are held to be more exalted fields. This dubiety arises from ignorance and from a conservatism which reflects no glory on its adherents.

My own view is that the profession of industrial doctor is being developed on lines which may be criticized and the man himself may suffer as a result. But the work to which he directs himself is vital to the development of the industrial society to which we are committed. He has to contend with the vagaries of employers, workers, engineers, administrators, departments of welfare, both in his factories and in the trade unions, and has to maintain a balanced calm and impartiality in the midst of conflicting interests. He has to deal with minds and bodies. He has to think of his people not in the brief period of a consultation, but throughout the day and night of their work.

His wounded in the field have to be sent to other parts of the field or back to the same sector; his preoccupation is not ended by his cure of them. This is the man who must know about all the activities in his factories and be able to make a judgement on the impacts of them on his human subjects. The condemned paternalism of the industrial past has changed into his beneficent paternalism of the present. This man must be as knowledgeable about things and methods as he is about the signs and symptoms of deflections from the normal.

He is the link with the industrial toxicologist and the interpreter to his managements. He poses problems, utters doubts, expresses impressions, hopes for interpretable measurement, carries clinical pictures in his mind which he may be unable to describe, looks in perplexity at the statistician's esoteric antics, begs for antidotes and effective therapies, prays that his first-aid teams will not let him down, pursues the often tedious path of maintenance of efficiency and readiness in services which may have only the rarest opportunity to show their prowess, and is often expected to know about and pronounce on the most varied matters which may appear irrelevant to his defined function.

This is the man who was regarded as the Cinderella of medical art and science. The picture is perhaps overdrawn, since many part-time doctors may also be busy practitioners, or may even not be permitted to enter the factories at all. But it certainly applies to the now large body of men who are wholly engaged in industrial medicine, and especially those who spend their days in hazardous industries.

The kind of observation and record he can make on the effects of toxic materials on human subjects is the essential basis of legislation and the protective measures that may be expected to follow upon it.

The Worker and the Animal in Industrial Toxicology

Whereas in experimental toxicology the animal is a passive instrument, this is far from the case in industrial toxicology in the field, and I therefore summarize briefly how the worker is different.

He should be told what the hazards are which he may encounter and what untoward event may follow. As I have advocated this course for many years, it is a satisfaction to note that Smith (1956) of the engineering and chemical branch of the

Factory Department made the following statement to the Institution of Chemical Engineers:

> We have not in Great Britain done very much so far to teach the ordinary workman the dangers of the materials and plant with which he is concerned, and the reasons that lie behind precautions to prevent injury or poisoning. We ought to do more [he continues] and we can learn a great deal from American authorities and from some of the big American companies.

It would be absurd to suppose that all workpeople are equally susceptible to information of this kind. In fact, it may very well be that those workers who are susceptible to such education are, on the whole, in little need of it, and vice versa. Workpeople must be taught by methods adapted to a practical level of comprehension by a combination of concrete illustration drawn from life and industry and positive action directed against the hazard under consideration. I consider exhortation of little value. One grain of positive action, well understood and approved by the man's common sense, is worth more than a granary full of exhortation introduced by biblical negatives.

If the information is absorbed, understood and approved, the workman will see the sense of medical and biochemical examinations which are often necessary to measure the extent to which protective measures are defective or deficient. He will, moreover, be more willing to disclose symptoms which are relevant and less likely to trump up imaginary complaints attributed to his work.

Let us admit that the often wilfully misleading attribution by workers of subjective symptoms to industrial products or processes is not more irritating than the humiliating obscurantism which so often attaches to terms which the doctor apparently authoritatively uses in his daily dilemma of having somehow to placate his patients or their relatives.

Human subjects vary to a much greater extent than do members of the same animal species, especially laboratory animals. For a population of humans, the scatter of doses (symptomatic, lethal, producing a measurable biochemical lesion, or pathological lesion) will be very great and much less so for animals. And hence, even were the mean values identical for men and animals, the application of data from animals to men must have regard to the relatively high standard deviation from the mean in human subjects. If we can assume a normal distribution, the loss at the lower doses will, as far as the whole population is concerned, be regained at the higher doses. Qualitative evidence for this proposition in the matter of toxic doses in industry is an everyday experience in factories and is often a source of both danger and dilemma. Men, whose sensitivity cannot be anticipated, enter sheds, or take part in processes under conditions not hitherto suspect and rapidly go down with a variety of symptoms depending upon the toxic agents involved. Rapid reaction to lead, aromatic amines and nitro compounds, chlorinated hydrocarbons, chlorinated aromatic amines, aromatic diamines, aromatic diisocyanates, chlorinated phenols, nitro derivatives of aliphatic polyhydric alcohols, phosphorus insecticides, etc., is a commonplace at levels of exposure or absorption regarded as tolerably satisfactory.

This is, in part, the result of the unavoidable employment of non-selected individuals. Experimental animals in numbers permitting statistical interpretation of results are a selected population usually bred for uniformity, and hence will show a much smaller concentration of individuals at both ends of the distribution curve.

It is difficult, perhaps impossible, to simulate with animals the conditions in which a worker may find himself. Injection or feeding experiments are of great value in elucidating the pathology and biochemistry of toxic effects (acute and chronic) and in obtaining the relative toxicities of different substances with similar actions, but their application to human subjects *in industrial conditions* or in everyday life calls for much additional evidence.

Intraperitoneal injection, although with no counterpart in human situations, is of value as in some sense simulating inhalation. But if injected in oily media, the rate of entry of the water-insoluble material into the circulation may be so slowed as to be misleading.

In the circumstances in which the effect of oral ingestion of substances by human subjects is at issue, the assumption must be made that man is much more susceptible than animals, perhaps tenfold or even a hundredfold more.

Inhalation experiments are more likely to have direct application to man, but animals are exposed usually in quiescence and bored fortitude, whereas man is exposed in conditions that entail differences in respiratory rates, energy expenditure, and variations in concentrations. The ingestion of alcohol and many other incalculable factors also affect his response.

Per cutem absorption experiments on animals are the easiest to interpret when positive, but considerable precaution is necessary to obviate per os absorption by licking. Negative or relatively negative results may be misleading unless temperature effects (of skin and of the material itself) are studied. Simulation of industrial conditions is closer if the materials used are rubbed in, but quantitation may be prejudiced if this is done.

The importance of temperature was well shown in a factory some years ago, where the handling of a low-melting *chlorinated aromatic amine* had proceeded for many years without anxiety. This continued until a normal batch was made and handled during an extremely hot August. The almost immediate consequence was an outbreak of violent *haemorrhagic cystitis*, without doubt following a greatly increased rate of absorption through the skin. Similarly, but more dangerously, the passage through a burnt skin surface is greatly accelerated. This was a factor in the recent death of a man following a not very extensive burn with hot chlorinated phenol.

The divergence of animal susceptibilities and metabolism from those of man is rendered less significant from our present point of view if several different species are used, rodent and non-rodent. The myth of the monkey need not be pursued if there is some consistency in the reactions of non-anthropoids.

The rat is still the most useful animal for our purpose—relatively cheaply maintained, it lives healthily in laboratory conditions, is easily multiplied, easily handled, gives consistent data, is readily used for metabolic and blood studies, is excellently adapted to inhalation, insufflation and all manner of injection experiments, consumes artificial diets at foreseeable levels, etc., etc. The great value of the rat lies in the fact t... for a given breed a body of knowledge of their 'normal pathology' can be built up, which helps to prevent misleading conclusions.

Animal experiment is essential to discover ultimate effects which may follow apparently unharmful exposures to and administrations of industrial materials since the animal can be observed for any desired time, or until death. Such discovery is incomparably more difficult for man.

The recent classic statistical studies of Case and his colleagues (1954) on the incidence of vesical tumours in the chemical industry illustrate the immense amount of work that may be necessary to establish a full statistical picture of an industrial disease and to make justifiable attributions. A workman is often mobile and what has resulted from one or more kinds of industrial exposure may never become known at all as he moves from place to place in the course of his working life. This adds immensely to the labour of collecting statistics. In my own experience certificates of natural causes have been given by practitioners who could have no inkling of the significance of studying the prior occupational history of the deceased and did not, of course, associate the diseases with it.

It is not, in general, a subject of investigation to discover the effect on immunity reactions of industrial toxic materials in animals or man. That certain industrial poisons can affect *complement*, *agglutinins*, *haemolysins* and *bacteriolysins* has been shown in respect of CO, C_6H_6, $HgCl_2$, $CaCN_2$, Pb, P, As, Mn, CCl_4, $K_2Cr_2O_7$, fluoride and thallium compounds. But much more work is required. That one kind of industrial lesion may predispose to infection is well recognized in the silicosis-tuberculosis relation, and evidence is accumulating that an asbestosis lung carcinoma relation exists.

Recent work on the effects on mitochondria of chlorinated hydrocarbons appears to show that these widely used industrial compounds act physically on these complex intracellular structures, detaching essential cellular coenzymes and thus breaking the Krebs cycle. Although mitochondria disintegrate in pathological conditions, it is not at present possible to say how far maintained absorption of industrial poisons may lead to irreversible deflections from normal function, not necessarily inconsonant with working capacity for a long time.

Without necessarily subscribing to the dark forebodings of the late Sir Edward Mellanby and, more recently, Sinclair (1956) as to the possible relation of food processing and food additives to the many diseases of unknown etiology, one can still consider it desirable to inquire more closely into the effect of industrial exposure on subsequent health.

There are many conflicts of evidence and it is exceptional to find an unequivocal case. Thus, in the matter of the so-called *Alkali Welding Rod*[1] which produces the best weld for many vital national purposes and which has been used for a good many years in other countries without undesirable effects, it is still claimed by operatives in this country that their health is somehow affected.

The impossibility of proof of a negative needs no emphasis here, but it may be said to those who are attracted to our field of work that this dilemma is one they will meet at every turn.

Chronic Effects of Industrial Toxic Agents

The proof that in industrial conditions a substance or process will have no deleterious effects on workpeople (and it may be permissible to say that work is not the exclusive prerogative of members of trade unions) rests either upon long experience in the field combined with extensive clinical record or upon the inferences which can be drawn from experiment.

From what criteria can the observer in the field draw the necessary conclusion as to the effects of chronic absorption? His conclusions, as we have already said, are the determinants of official or industrial action and, with the authority of medical responsibility, will exert greatest influence on the apprehensions of workers in a given case.

The classification of workers into groups according to significant hazard may be more difficult than at first sight appears. Where many chemical hazards exist many men may belong to several

[1] Basic coated low-hydrogen electrodes.

groups. Many may be exposed even if their jobs are elsewhere than where the hazard exists. Workers in factory laundries may be exposed. Thus, it may become necessary to create sub-groups according to the estimated degree of potential hazard. I may recall, in passing, the cases of two young women who died from organic mercurial poisoning after having worked as typists in a room adjacent to a packing department, and of men who developed occupational cancer through exposure to fume from an adjacent building.

It is an old dictum of pathologists that on the whole you find what you are looking for. That is to say, as one examines a tissue or organ or histological slide, one must be constantly repeating in the mind: 'Is there this present or that present?' In industrial problems *it is necessary to establish not only that this or that is present, but that it is related to a particular substance or process*, and that it occurs very significantly more frequently among particular groups than among others.

Medical record should include not only the clinical examination of the various systems, circulatory, respiratory, blood, nervous, excretory, digestive, muscular, etc., but also the difficult questions of fatigue, working capacity and efficiency, sleep, zest, interest, appetite and gastric content, memory, emotion, and other elements in the psycho-organic field; i.e. symptoms and signs simulating organic disease but deriving from mental disturbances of function with an as yet unknown pathological-physiological basis. I am concerned here to emphasize that the common practice of dismissing many of the subjective complaints of workers should be discouraged. This practice is discernible even where blatant industrial poisoning is foreseeable. On a recent visit to a lead mill, for instance, I asked the manager whether his men complained of anything. His reply was that some of them had occasionally complained of 'belly-ache', but there was nothing to it. Shortly thereafter two men went down with all the signs and 65 per cent Hb.

Some twenty years ago it was proposed by Smyth, Smyth and Carpenter (1936) in the U.S.A. that for CCl_4 a concentration of 100 p.p.m. in the working environment was permissible. Six years later Elkins (1942) found in various kinds of operation involving CCl_4 that such symptoms as nausea, belching, drowsiness, tiredness, headache, might each or all occur at average concentrations between 20 and 85 p.p.m. The important point was the frequency of entirely subjective symptoms, nausea and headache, with 'little objective evidence of injury'. Two years later Stewart and Witts (1944) described cases of CCl_4 absorption among workers engaged in the chlorination of an aromatic amine dissolved in CCl_4. The remarkable thing about these cases was that in spite of a variable gastro-intestinal and cerebral symptom-complex (nausea, anorexia, abdominal pain, diarrhoea, sometimes vomiting, haematemesis and even rectal bleeding, weakness, dizziness, confusion, headache, dyspnoea, cough, loss of weight) it was, the authors stated, difficult to believe that they were ill at all.

In my own experience of factories where, during the war, ethylene chlorhydrin was manufactured in large quantities, and where the machinery and reaction vessels were so closely crowded together that pockets of considerable concentrations were built up, men and women workers without complaint would periodically leave the sheds and have a quiet, secluded and furtive vomit. It was only when one worker made a mild complaint of nausea that the situation was exposed, but unfortunately not before another worker had suffered long enough to develop a chronic nephritis which killed him. It was manifest that the workers for reasons which might have related to the high rates of pay were loath to report what appeared to them to be minor symptoms.

A recent comment by investigators in Holland (Frant and Westendorp, 1950) on the significance of the urinary concentration of trichloracetic acid in workers exposed to trichloroethylene was that 'continuous contact may familiarize a workman with the symptoms of drowsiness, dizziness, etc., and this may cause him to neglect them'. Very recently (Grandjean *et al.*, 1955) a group of Swiss workers submitted men exposed to trichloroethylene to a detailed psychiatric examination (fixation memory, attention, comprehension, ideation, affectivity) and claimed that elements something akin to the Korsakow psychosis could be established in increasing frequency among workers as the concentrations in which they had worked rose from 14 p.p.m. to 34 p.p.m. to 40 p.p.m.[1]

It is too early to be sure about this work, but it seems desirable to consider where psychiatric tests stand in the routine of industrial toxicology. Our present criticism of the above observations rests upon the inadequate control data, the fact that the incidence and intensity of subjective symptoms were not greater among men exposed to the higher concentration for longer periods than among those exposed to much milder conditions.

The third criterion to which particular attention is now drawn is the degree of contamination of the environment in which the affected persons worked. By the time adverse effects have become manifest it is possible only to try to prevent further trouble. This is the domain of what has been called the *maximum allowable concentration.*

It is well to realize the following facts and queries:

(1) A maximum allowable concentration has no legal sanction. Where legal sanction has been tried, either methods of determination were found inadequate or the circumvention of the enactment was child's play.

(2) The maximum allowable concentration values are thus referred to by Cook, a noted worker in this field:

> It is to be emphasized that the intent in presenting these maximum allowable concentrations is to provide a handy yardstick to be used as guidance for the routine industrial control of these health hazards—not that compliance with the figures listed would guarantee protection against ill-health on the part of exposed workers, nor should the maintenance of the suggested concentrations be considered a substitute for medical control.

This is a very cautious statement.

Annual review of the 'maximum average atmospheric concentration of contaminants to which workers may be exposed for an eight-hour working day without injury to health' by the American Conference of Governmental Industrial Hygienists assures the most up-to-date values, from 'industrial experience,

[1] The classic Korsakow syndrome in alcoholism may also be simulated in chronic lead and mercury poisoning. Irritability, forgetfulness, change in moral character, impaired judgement, enfeebled will, false ideas of position in time and space, fabulous explanations of real occurrences, peripheral neuritis.

from experimental studies and, when possible, from a combination of the two'.[1] No such review by a responsible official body in this country is available. This is in accordance with the British tradition of avoidance of permissive clauses.

(3) Speaking of the American use of maximum allowable concentration values, Smith (loc. cit.) says:

> These figures, based partly on animal experiments and partly on industrial data obtained from animal experiments, cannot always be interpreted accurately in terms of human response because the quantitative industrial experience is incomplete.
>
> The misuse of the maximum allowable concentration lies in the fact that there seems to be a tendency for some of the industrial hygienists to take samples which may or may not be truly representative of the air breathed, to analyse these samples, and, if the results are below the arbitrary maximum allowable concentration, to assume that no further action is required. This may occur even where further improvement in a process, from the aspect of the health of the operatives, could be secured fairly easily.

(4) Of the enormous numbers of places where chemical compounds contaminate the atmosphere, in how many are routine analyses carried out? Very few, we may be sure. And how futile are the hysterical efforts to establish the atmospheric concentration after a case of poisoning or disease has occurred!

(5) What is the relation between the universal preoccupation with small amounts of food additives (apart altogether from those which are banned because they might obscure bacterial decomposition) and that with the maintained absorption for perhaps 30 or 40 hours a week by workers of small amounts of substances of incomparably greater potency?

Men who would be much concerned by the disclosure that if their whole diet consisted of lollipops they would ingest a few milligrams of a synthetic dyestuff, would hardly be worried at all by a much more significant disclosure relating to their work, where entry into the circulation through the skin or respiratory tract may be extremely rapid. We seem to have a long way to go before the strictures applied to the one should at the very least apply to the other.

[1] For 1955 list, see *Proceedings of 17th Annual Meeting of the American Conference of Governmental Industrial Hygienists*, Buffalo, 24–28 April 1955.

(6) Sickness absence records in factories are not, in general, a sufficiently sensitive index of the kind of signs and symptoms to which reference has already been made. A man goes off sick almost invariably because he is too ill to work. The effects we must seek to recognize are those which reflect upon well-being, efficiency and perhaps on accident incidence, rather than on the grosser criteria of manifest illness.

It will, perhaps, be best to seek in the realm of social relations for evidence of home contentment, zest and interest in both work and leisure, vague discomforts and dysfunction, disturbance of normal sleep and difficulties called psychological. It will depend a good deal upon the kind of industry being studied as to the effects of predominantly subjective complaints on efficiency and productivity. Some recent studies in the accumulator industry led to the observation that: '. . . neither psychological handicap nor mental ability affected productivity in all groups as much as social background in the home and in the factory'; and again 'the assumption that workers who have a psychological handicap such as neurosis produce less than the average worker was not confirmed in this limited study of 80 workers' (Markowe and Barber, 1952).

The same observers also found in the same industry that in comparing two groups of workers as to productivity, it was the more mentally healthy and more effective group which had by far the greater sickness absenteeism (5:1). It may be that ability and efficiency go hand in hand with a measure of hypochondriasis and, if so, confusions would arise in factories possessing toxic hazards.

Requirements if Prevention of Chronic Toxic Effects is to be Attained

There are so many chemical elements and compounds which in sufficient concentration produce manifest effects on physiological, metabolic, enzyme, hormone and other systems that the least we must ask for those exposed repeatedly to any concentrations includes:

(a) determination of the atmospheric concentrations at appropriate points and as a routine;

(b) development of simple but sufficiently reliable methods of analysis suitable for field application;

(c) recognition by industrialists, small or big, that such work is part of industrial processes;

(d) routine examination of workers for relevant signs, symptoms or biochemical changes;

(e) in appropriate cases, chemical examination of urine for metabolites, metals, or cellular abnormalities;

(f) institution at appropriate centres of investigations into the toxicological and pathological effects of new or old materials;

(g) recent developments in other countries indicate that a more drastic approach is being made to the dilemma of applying experimental results to man.

In at least four cases data are being sought by:

(i) exposing working volunteers to atmospheres containing organic phosphorus insecticide;

(ii) exposing working men in specially enclosed workshops for eight hours a day five days a week to controllable concentrations of lead or fluoride;

(iii) volunteers are also being fed diets containing lead or fluorides or other known toxic substances;

(iv) the toxicology section of the United States Public Health Service has reported experiments on 51 volunteers who consumed DDT (35 mg. per man per day) for from one month to one year (Hayes *et al.*, American Association for the Advancement of Science, quoted in *Chemical Trade Journal*, 1956).

This kind of work will, of course, provide data on normal tolerances, normal metabolic or detoxicating mechanisms, rates of excretion or retention, rates of recovery of inhibited enzyme systems, effects of therapeutic agents of the chelate type and, no doubt, much else, but it cannot replace the field work already mentioned.

This list is bound to be regarded as formidable to the small employer or even to the not so small man but, in fact, trade organizations are becoming more and more conscious of the need for such work. Even government departments (e.g. D.S.I.R.) are considering establishing laboratories for these purposes in collaboration with industry.

At the moment in this country only two or three laboratories exist for this purpose, the Medical Research Council laboratories under Dr. John Barnes, where there is a strong and impressive pharmacological rather than industrial predilection; the Medical Research Council unit under Dr. Hunter, where there is a strong clinical (but perhaps less marked pharmacological and industrial) activity; and the laboratory of Dr. Edson who exerts a most careful scrutiny of insecticidal and fungicidal products. University departments on occasion undertake *ad hoc* studies for particular industries and naturally have an academic approach.

Imperial Chemical Industries have established laboratories employing between thirty and forty persons and the points I have indicated are dealt with not only in the laboratory, but in the field in close collaboration with the many medical officers in the numerous factories of the company. A large body of literature, experimental, clinical and industrial information has been built up. The accumulated experience and knowledge of our scientific staff is frequently consulted by government and industrial bodies and our willingness to discuss and help is dictated solely by their earnestness in the promotion of health and safety in the factory.

Increasing knowledge of the manifold subtle effects of industrial toxic materials has brought to light much that was unknown or obscure even a short time ago. The constant review of maximum allowable concentration values which is practised in the United States of America is indication enough that in respect of atmospheric contaminants doubts may enter at any time as clinical field-experience increases.

The nuclear age is calling for the use of more and more of the rarer elements, the toxicological properties of which are still unknown. The organic chemist produces new compounds more quickly than they can be studied and the urge for rapidly delivered toxicological information may induce a tendency to be satisfied with insufficient and superficial experiment. Moreover, the toxicological data must be combined with the manner of use of materials, the place of use and the working conditions in order to enable a reasonable course to be steered in the factory.

Above all, the hazard of applying data from animal experiment to men must be reduced to a minimum. This hazard is variable and should induce a respect for Belloc's bright couplet:

Let us never, never doubt
What nobody is sure about.

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XVI

The Nutrition of Micro-Organisms

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Effect of Physiological State and Environment on Nutrient Needs

All living organisms require water, an assimilable source of energy and sources of organic compounds and of minerals for growth. Most investigations into the nutrient needs of micro-organisms have been concerned with requirements for growth and reproduction, i.e. completion of the whole life-cycle, but it is important to remember that the needs may often vary with physiological state and metabolic activity; e.g. the requirements of the germinating spore differ from those of the vegetative phase. Similarly the medium constituents necessary for most rapid growth of *Penicillium* species can be very different from those that may stimulate the productive organism to maximum penicillin production.

Environmental factors, such as light, temperature, osmotic pressure, pH, redox potential and oxygen supply, are frequently important not only for growth rate but also for nutrient needs. For instance the absence of light may drastically modify the requirements of photsynthetic organisms, oxygenation may modify vitamin B_{12} requirements and changes in temperature can abolish the adenine dependence of certain mutant strains of *Neurospora*.

Utility of Nutritional Studies

Knowledge of the requirements of micro-organisms simplifies their maintenance in controlled populations under precisely defined conditions. At the same time nutritional information