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RESEARCH IN INDUSTRIAL HEALTH IN THE CHEMICAL INDUSTRY *

BY

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The satisfaction I feel at the opportunity afforded me to add my homage to that of old colleagues who have preceded me in the commemoration of James Mackenzie and his work is of a special kind. Mackenzie was a man with a mission. He also had a vocation, and his life was rich in worth. If James Mackenzie sought to bring what might be called "physical" light to the dark and sick lives of the industrial workers of his time, he brought much spiritual light also. To have enlisted the cooperation of some of the most notable and busy men in public health and medicine through his Industrial Health Education Society required qualities which, when they impinge on other men's minds, raise them to heights they would never wish to leave. These qualities of Mackenzie are those which every medical officer in industry requires.

The workers and staff of an industry are in a real sense the flock of the industrial doctor, and he should be as preoccupied about their physical and mental well-being as the parson is presumed to be about the spiritual life of his flock. His factory is his industrial health education society, but there the people to be taught are not only the workers but the employers also.

Thirty years ago, when James Mackenzie was founding his society, industrial medicine was in the stage of exhortation. The workman was suspicious of the "compo" doctor; the employer might employ a doctor to examine new entrants, for first-aid services, and in compensation cases. Many doctors thus appointed were not permitted to enter the factories at all. The health and well-being of a worker were then of consideration only as they might affect the employer's interests. Then, as now, the appointment of an industrial medical officer and what he was asked to do lay with the employer.

The coming of the second world war gave an impetus to industrial medicine in this country and in many others for which the workers may be thankful. Practitioners now visit factories, join in lectures and discussions, avail themselves of services provided by industry in the factories, and exchange information with the industrial doctor. To-day the stage of exhortation is almost over.

James Mackenzie died in 1944, his society having been wound up at the beginning of the war, but he must have seen the movement towards more and more social realization of responsibility for the health of the nation in a sense more profound than it had ever been. My own satisfaction in paying my tribute to Mackenzie consists in the knowledge that after following with so many of my friends his path in the health education of the worker and his employer I was put in charge of the first industrial hygiene laboratories established by industry in this country, a tangible proof of the awakened realization among industrialists that industrial health is not a question of policy, but one of science, of conscience, and of civility.

Maximum Allowable Concentration of Atmospheric Contaminants in the Working Environment

For an industrial environment where harmful elements, compounds, or radiations are known to be actually or potentially present, it has become customary to prescribe an allowable concentration of dust, gas, fume, or vapour which must not be exceeded if an assurance is sought that men and women may work in that environment without harm. Perhaps more customary in the U.S.A. than in Britain, the term "maximum allowable concentration" (or variants of it) is becoming more familiar here also. It may be recalled that the conception was foreshadowed in this country by Thomas Legge some 45 years ago when he (and Duckering) gave 5 mg./10 cm. as the atmospheric concentration of

* The Mackenzie Industrial Health Lecture delivered in Manchester on July 13, 1954, at the Annual Provincial Meeting of the Association of Industrial Medical Officers.

lead in which engineers and chemists might work. By prescribing a maximum intake of lead, however, there is the implication that the harder a man works in the atmosphere containing lead, the shorter time he should be permitted to do so. Thus, merely to give a maximum permissible concentration without giving the severity of the work and the time engaged per day in such work, leaves one entirely in the dark as to what a man is absorbing. Lane (1949) and Kehoe (1949) substantially agree that at 1·5 to 2 mg./10 cm. " cases of disabling lead intoxication do not occur among men who work regularly in such workrooms, and cases of questionable or mild intoxications are rare ".

But Lane is not slavishly attached to this maximum allowable concentration and insists (*loc. cit.*) that the final test must be the effect on the workmen and, by implication, that mere analysis of the atmosphere is not enough. This statement is of great general significance and may be considered in conjunction with the views of Cook (1945), one of the distinguished workers in the field of maximum allowable concentrations. Cook says :

> " It is to be emphasized that the intent in presenting the 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."

The use of the words " suggested concentration " is a sufficient indication that the conception is not precise.

Drinker and Cook (1949) in a later contribution emphasized, by implication, the imprecise nature of these concentrations when they proposed a zoning system, whereby, it was stated, the toxicity of an industrial atmospheric contaminant could be quickly assessed from the zone in which it falls. Six zones were given as follows :—

500–2,000 p.p.m.	acetone, petrol, ether
100– 500 p.p.m.	methanol, toluene
20– 100 p.p.m.	benzene, butanol, CCl_4, CO
2– 20 p.p.m.	H_2S, CS_2, C_6H_5Cl, HCl, HCN
0·1– 2 p.p.m.	Cl, $COCl_2$, AsH_3, $(CH_3)_2SO_4$
0·1 p.p.m.	radon, radioactive gases, etc.

They added : " The zoning scheme is for the classification of information and not for the justification of excessive exposure or misguided legal interpretation."

Tables of maximum allowable concentrations must not evoke responses which are entirely unjustified and even dangerous. Classification in zones cannot fail to influence non-medical personnel by suggesting similar toxicities of substances, the effects of which are entirely different. For a doctor the association of a hazard with a value or a zone of values is desirable to supplement the picture already in his mind of one or more features of the effects of the compounds. Non-medical personnel, however, are not as a rule in the same position. They are likely to use, and in fact do use, phrases such as " Arsine—oh yes, about as toxic as bromine, isn't it ? ", or, " Tetrachloroethane—yes, yes, quite troublesome—about as bad as hydrochloric acid ", because, in fact, their maximum allowable concentration values are identical, but, it must be noted, for very different reasons. Toxic hazards should, in general, be considered as identities with their own numerical data attached to them and their own effects attached to the numerical data.

Hazards may have to be classified into groups for convenience or as aids to memory, but this must be on the basis of similarity of toxic effects and not on the fortuitous closeness of maximum allowable concentrations.

The fact that both HCl and HCN are in the same Drinker and Cook zone (2–20 p.p.m.) as aniline, acetic acid, and acrylonitrile tells us nothing of their effects or relative dangers. This is even more strongly illustrated in the highly dangerous zone 0·1–2 p.p.m.

DRINKER AND COOK ZONES (EXPANDED)

0·1 p.p.m.	0·5 p.p.m.	1·0 p.p.m.	2·0 p.p.m.
Hydrogen selenide Iodine Stibine	Arsine Bromine Cyanogen chloride Ethyleneglycol dinitrate Phosgene Phosphorus trichloride Ketene Nitroglycerine	Chlorine Hydrazoic acid	*p*-Chloraniline *p*-Chlor-nitrobenzene Ethylene chlorohydrin Hydrogen fluoride

N.B.—HCN 10 p.p.m.

In this table we have some of the most fulminating poisons met with in industry, and it would be in the highest degree undesirable to bracket them together in any sense whatever. For, whereas some of the limits set are those for immediate irritation, others are for delayed effects, and others again for cumulative effects. Some appear because of their effects on the circulatory mechanics ; others because of the effects of their metabolic products on haemoglobin : still others because they cause a dangerous increase of the permeability of the pulmonary vessels ; and others because of disruptive effects on the envelope of the blood corpuscles.

So diverse a picture demands different degrees of urgency in persons whose responsibility it is to prevent concentrations above those prescribed. Moreover, the sense of urgency must clearly depend also on the physical pic involved. Everyone con scious of clinical urgency urgency. The state of m approach to environme implied in the table of my laboratories (Table I

The actual values give in the light of experien emerged from a search and experimental record likely. Still, some hav example, in the case ammonia, ethanol.

The first three column by certain concentration dangerous symptoms ; concentrations which a two columns give conce limit to satisfactory c particular substance (de

The use of the wo concentration " has be we hold that no conce are worse than others

Animal

For industrial toxicol to use animals in expe conditions. Most in result of absorption b much more rarely by i most, acute and chronic Very little is known c substance thus absorbe

Factors of safety m animal experiments a depending upon man upon his greater activit can be made of the am absorbed by men at environmental condit estimated by exposing estimate. Since the n many times greater th fume concentrations without adverse effec as equally inoffensive concerned.

Cutaneous absorp great importance in and in the field use o and herbicides.

Quantitative meas neous absorption in

also on the physical properties of the compounds involved. Everyone concerned must be made conscious of clinical urgency as well as of quantitative urgency. The state of mind which informs our own approach to environmental contaminants is that implied in the table of concentrations issued from my laboratories (Table 1).

The actual values given may require modification in the light of experience, but as each figure has emerged from a searching examination of clinical and experimental records, great modifications are not likely. Still, some have already been made; for example, in the case of formaldehyde, acetone, ammonia, ethanol.

The first three columns indicate the times required by certain concentrations to produce very severe and dangerous symptoms; the next two columns give concentrations which are not tolerated; the last two columns give concentrations which set an upper limit to satisfactory conditions in respect of the particular substance (design concentrations).

The use of the words "maximum allowable concentration" has been avoided because at I.C.I. we hold that no concentration is allowable. Some are worse than others but all are bad.

Animal Experiment

For industrial toxicological purposes it is important to use animals in experiments simulating industrial conditions. Most industrial poisonings are the result of absorption by inhalation or by the skin, much more rarely by ingestion and by the eyes, and most, acute and chronic, are to mixtures of substances. Very little is known of the adjuvant effects of one substance thus absorbed on the toxic effects of others.

Factors of safety must be assumed if results of animal experiments are applied to man, factors depending upon man's greater susceptibility and upon his greater activity during work. If an estimate can be made of the amount of a toxic substance daily absorbed by men at work, the acceptability of the environmental conditions in which it occurs can be estimated by exposing animals to multiples of that estimate. Since the metabolism of small animals is many times greater than that of man, gas, vapour, or fume concentrations at which animals can subsist without adverse effects may be reasonably regarded as equally inoffensive to man as far as overt signs are concerned.

Cutaneous absorption of toxic materials is of great importance in the organic chemical industry and in the field use of toxic insecticides, fungicides, and herbicides.

Quantitative measurement of the degree of cutaneous absorption in animals is difficult, but comparative measurements can be made with small animals by time measurements from the onset of symptoms to death, or to measurable biochemical effects after immersion of anatomical appendages, such as paws or tails, in known concentrations of the compounds studied. Many substances are more toxic cutaneously than orally.

The demonstration of dermatitic effects in animals which do not perspire in any sense similar to that seen in man is usually impossible although an urticaria-like reaction is sometimes seen. The phenomena of "contact dermatitis", "sensitization dermatitis", "allergic dermatitis", or "eczema" are not reproducible in animals in experimental conditions. Complicated immunological demonstrations that some chemical compounds can act in appropriate conditions as skin allergens are possible and such demonstrations have corresponded with the known properties of some organic compounds. Erythema and oedema should be measured according to determined scales (Draize, Woodard, and Calvery, 1944). The skin of laboratory animals does not respond as does human skin to the host of chemical substances which induce dermatitis of the acute variety so frequently seen in industrial conditions. In the case of cutaneous cancer the correspondence is closer. Thus, animal experiment is largely directed to finding whether given chemical compounds induce direct irritant effects on the skin.

Physiological effects (on the circulation, respiration, blood pigments, tissue and blood enzymes, renal and hepatic function, growth, fertility, central nervous system), in the sense of reversible effects, can be demonstrated by animal experiment with relative ease, and the results in some cases applied to the clinical control of hazards in the factory. Contact dermatitis in man disappears on removal from exposure, but the effect is not truly reversible.

A fall in blood pressure, readily demonstrable in animals, is used by some American authorities as a clinical-statistical index of undue absorption of many toxic organic compounds. There are some explosive compounds (made and used both here and in other countries) which are rapidly hypotensive in working conditions: blood pressure determinations are essential for proper medical control in these cases, especially as pseudo-anginal attacks may follow long-term exposure. Many industrial compounds can be shown experimentally to depress the heart, dilate the peripheral vessels, or increase vascular permeability. Others, by cholinesterase inhibition, lead to parasympathetic stimulation and vagal effects on the heart. The question of the establishment of hypertension, perhaps of renal origin, in chronic lead absorption is not resolved.

TABLE I

TOXIC CONCENTRATIONS OF VARIOUS GASES, DUSTS, FUMES, AND METALS IN THE ATMOSPHERE

(I.C.I. Industrial Products and Health Research Committee)

No.	Gas	(1) Concentrations Causing Severe Toxic Effects in Persons Exposed for the Stated Times			(2) Concentrations which, if Exposure Continues for more than a Short Time, may Lead to Symptoms of Illness		(3) Concentrations in General Atmosphere of Plant Greater than those below Indicate Unsatisfactory Conditions	
		(p.p.m. v/v)	(mg./cu.* metre 20°C.)	Time of Exposure (Min.)	(p.p.m. v/v)	(mg./cu.* metre 20°C.)	(p.p.m. v/v)	(mg./cu.* metre 20°C.)
1	Acetaldehyde	1,000	1,830	60	500	915	200	366
2	Acetic acid	200	500	60	40	100	20	50
3	Acetone	4,000	9,630	60	800	1,930	400	963
4	Acetone cyanohydrin	40	140	1	20	70	10	33
5	Acetonyl acetone	300	1,424	60	150	712	30	356
6	Acetophenone	80	400	60	40	200	20	100
7	Acetyl chloride	10	33	1	2	6·6	1	3·3
8	Acrolein	20	46	1	8	18·6	3	11·6
9	Acrylonitrile	100	220	1	50	110	20	44
10	Allyl alcohol	40	96	1	20	48	5	12
11	Allyl chloride	200	636	60	100	318	50	159
12	Ammonia	500	355	1	200	142	100	71
13	iso Amyl acetate	1,000	5,410	60	300	1,623	100	541
14	iso Amyl alcohol	400	1,464	60	200	732	100	366
15	Aniline	80	312	60	20	78	10	39
16	Arcton 6 (Freon 12) (Difluorodichloromethane)	50,000	251,700	60	20,000	100,680	10,000	50,340
17	Arsine	10	32	1	1	3·2	0·5	1·6
18	Benzene (Benzol)	1,500	4,800	60	500	1,600	50	160
19	Benzine (as Hexane)	3,000	10,728	60	1,000	3,576	150	594
20	Benzyl acetate	100	616	60	50	313	15	94
21	Benzyl chloride	20	100	1	10	50	2	25
22	Bromine	1	20	1	1	6·6	0·5	3·3
23	Butadiene	8,000	17,968	60	5,000	11,230	2,500	5,615
24	n-Butanol (Butyl alcohol)	1,000	3,080	60	100	308	50	154
25	2-Butanone (Methyl ethyl ketone)	See No. 90 Methyl ethyl ketone						
26	n-Butyl acetate	2,000	9,650	60	500	2,412	200	965
27	n-Butyl methacrylate	800	4,724	60	400	2,362	200	1,181
28	Carbon dioxide	30,000	54,930	60	10,000	18,310	5,000	9,155
29	Carbon disulphide	500	1,600	60	150	480	30	96
30	Carbon monoxide	400	464	60	100	116	30	34
31	Carbon tetrachloride	2,000	12,800	60	500	3,200	50	320
32	p-Chloraniline	8	44	1	4	22	2	11
33	(mono) Chlorobenzene	400	1,872	60	200	936	75	351
34	2-Chlorobutadiene	100	368	1	50	184	25	92
35	Chlorine	10	29	1	4	12	1	2·9
36	p-Chloronitrobenzene	10	66	1	4	26	1	6·6
37	Chloroform	2,000	9,960	60	500	2,490	50	249
38	(o & p) (mono) Chlorotoluene	400	2,106	60	200	1,053	75	395
39	Cyanogen chloride	5	13	1	2	5·2	0·5	1·3
40	Cyclohexane	2,000	6,990	60	800	2,796	400	1,398
41	Cyclohexanol	1,000	4,160	60	400	1,664	100	416
42	Cyclohexanone	1,000	4,080	60	200	816	75	306
43	Cyclohexylamine	100	410	1	40	164	20	82
44	p-Dichlorobenzene	300	1,836	60	100	612	25	153
45	2,2'Dichlorodiethyl ether	100	593	1	10	178	15	89
46	(cis & trans) Dichloroethylene	2,000	8,072	60	1,000	4,036	300	2,018
47	Dicyclohexylamine	50	388	60	40	302	20	151
48	Diethyl carbonate	800	3,928	60	400	1,964	200	982
49	Diisobutylene	4,000	18,640	60	2,000	9,320	1,000	4,660
50	Diisobutyl ketone	400	1,896	60	200	948	100	474
51	Dimethyl dioxane	500	2,412	60	300	1,447	200	965
52	Dimethyl sulphate	15	78	1	10	52	2	10
53	Dioxane	500	1,830	60	300	1,098	200	732
54	Ethanol (Ethyl alcohol)	8,000	15,312	60	2,000	3,828	1,000	1,914
55	Ether (diEthyl)	8,000	24,624	60	2,000	6,156	500	1,539
56	β-Ethoxyethyl methacrylate	500	3,285	60	200	1,314	100	657
57	Ethyl acetate	2,000	7,320	60	800	2,928	400	1,464
58	Ethyl acetoacetate	200	1,080	60	100	540	50	270
59	Ethyl benzoate	200	1,241	60	100	624	50	312
60	Ethyl bromide	250	1,115	60	100	454	50	227
61	Ethyl chloride	10,000	26,830	60	5,000	13,415	2,000	5,366
62	Ethylene chlorhydrin	20	68	60	10	34	2	7
63	Ethylene dichloride	500	2,050	60	100	410	30	205
64	Ethylene glycol dinitrate	20	128	60	1	6·4	0·5	3·2

Concentrations shown in italic are tentative and are issued as a guide. Figures in all columns will be subject to review as more data become available.

* 1 mg./cu. metre = 4·37 x 10^{-4} grains/cu. ft.

Continued

No.	Gas
65	Ethylene oxide
66	Ethyl formate
67	Ethylidene dichloride
68	Ethyl silicate
69	Formaldehyde
—	Freon 12 (Arcton 6)
70	Hydrazoic acid
71	Hydrogen chloride
72	Hydrogen cyanide
73	Hydrogen fluoride
74	Hydrogen selenide
75	Hydrogen sulphide
76	Iodine
77	Isophorone
78	Ketene
79	Lauryl mercaptan
80	Mesityl oxide
81	Methacrylic acid
82	Methallyl alcohol
83	Methanol (Methyl alcohol)
84	Methyl acetate
85	Methyl acrylate
86	Methyl bromide
87	Methyl iso-butyl ketone
88	Methyl α-chloracrylate
89	Methyl chloride
90	Methyl ethyl ketone (2-B...
91	Methyl iodide
92	Methyl cyclohexanone
93	Methylene chloride
94	Methyl formate
95	Methyl methacrylate
96	Naphtha distillate (as C...
97	Nickel carbonyl
98	Nitrobenzene
99	Nitroethane
100	Nitrous fumes (as NO_2)
101	Nitroglycerine
102	Nitromethane
103	1-Nitropropane
104	2-Nitropropane
105	o-Nitrotoluene
106	Perchloroethylene (Tetr...
107	β-Propiolactone
108	iso-Propyl alcohol
109	Phosgene
110	Phosphorus trichloride
111	Stibine
112	Styrene
113	Sulphur dioxide
114	Sulphur monochloride
115	Sulphuryl chloride
116	Tetrachloroethane
—	Tetrachloroethylene (P...
117	Thionyl chloride
118	Thiophosphoryl chloride
119	Trichloroethylene
120	Toluene (Toluol)
121	(o, m, & p) Toluidines
122	Vinyl chloride
123	Xylenes (Xylols)
124	Xylidines
125	Antimony (dust or sa...
126	Arsenious oxide
127	Barium salts (as Ba)

Concentrations shown in ... become available.

Table I continued

No.	Gas	(1) Concentrations Causing Severe Toxic Effects in Persons Exposed for the Stated Times			(2) Concentrations, which, if Exposure Continues for more than a Short Time, may Lead to Symptoms of Illness		(3) Concentrations in General Atmosphere of Plant Greater than those below Indicate Unsatisfactory Conditions	
		(p.p.m. v/v)	(mg./cu.* metre 20°C.)	Time of Exposure (Min.)	(p.p.m. v/v)	(mg./cu.* metre 20°C.)	(p.p.m. v/v)	(mg./cu.* metre 20°C.)
[illegible]	Ethylene oxide	250	450	60	100	180	10	18
[illegible]	Ethyl formate	1,000	3,080	60	400	1,232	200	616
[illegible]	Ethylidene dichloride	400	1,648	60	200	824	50	206
[illegible]	Ethyl silicate	400	3,464	60	200	1,732	100	866
[illegible]	Formaldehyde	100	120	1	30	36	10	12
—	Freon 12 (Arcton 6)	See No. 16 Arcton 6.						
[illegible]	Hydrazoic acid	10	18	60	4	7·2	1	1·8
[illegible]	Hydrogen chloride	50	75	1	20	30	10	15
71	Hydrogen cyanide	40	44	1	20	22	10	11
[illegible]	Hydrogen fluoride	40	34	1	10	8·5	2	1·7
[illegible]	Hydrogen selenide	2	6	1	0·5	1·5	0·1	0·3
[illegible]	Hydrogen sulphide	200	280	1	50	70	20	28
[illegible]	Iodine	0·5	5·5	1	0·2	2·2	0·1	1·1
[illegible]	Isophorone	40	228	60	20	114	10	57
[illegible]	Ketene	2	3·6	1	1	1·8	0·5	0·9
[illegible]	Lauryl mercaptan	20	168	1	10	84	5	42
[illegible]	Mesityl oxide	200	816	1	100	408	50	204
[illegible]	Methacrolein	10	29	1	5	15	2	6
[illegible]	Methacrylic acid	1,000	3,575	1	400	1,430	200	715
[illegible]	Methallyl alcohol	150	450	1	100	300	50	150
[illegible]	Methanol (Methyl alcohol)	2,000	2,560	60	500	640	200	256
[illegible]	Methyl acetate	300	1,540	60	200	616	100	308
[illegible]	Methyl acrylate	100	356	1	50	178	25	89
[illegible]	Methyl bromide	250	1,000	1	50	200	20	80
[illegible]	Methyl *iso*-butyl ketone	1,000	4,160	60	400	1,664	200	832
[illegible]	Methyl α-chloracrylate	4	20	1	2	10	1	5
[illegible]	Methyl chloride	1,500	3,150	60	500	1,050	100	210
90	Methyl ethyl ketone (2-Butanone)	2,000	5,990	60	500	1,498	200	599
91	Methyl iodide	40	236	1	20	118	10	59
92	Methyl cyclohexanone	100	1,400	60	150	210	75	330
93	Methylene chloride	2,000	7,072	60	1,000	3,536	500	1,768
94	Methyl formate	1,000	2,495	60	400	998	200	499
95	Methyl methacrylate	3,000	12,480	60	2,000	8,320	1,000	4,160
96	Naphtha distillate (as Cumene)	300	1,500	60	150	750	50	250
[illegible]	Nickel carbonyl	4	28	1	2	14	1	7
[illegible]	Nitrobenzene	200	1,020	60	40	204	1	5·1
[illegible]	Nitroethane	800	2,496	60	500	1,560	200	624
100	Nitrous fumes (as NO_2)	100	190	1	30	57	10	19
101	Nitroglycerine	20	189	60	1	9·4	0·5	4·7
102	Nitromethane	800	2,028	60	500	1,268	200	507
103	1-Nitropropane	400	1,480	60	200	740	100	370
104	2-Nitropropane	400	1,480	60	200	740	100	370
105	o-Nitrotoluene	200	1,140	60	40	228	1	5·7
106	Perchloroethylene (Tetrachloroethylene)	1,000	6,905	60	400	2,762	200	1,381
107	β-Propiolactone	100	300	1	20	60	10	30
108	*iso*-Propyl alcohol	2,000	4,995	60	800	1,998	400	999
109	Phosgene	5	21	1	1	4·2	0·5	2·1
110	Phosphorus trichloride	2	12	1	1	5·8	0·5	2·9
111	Stibine	0·5	2·5	1	0·2	1	0·1	0·5
112	Styrene	1,000	4,330	60	200	866	100	433
113	Sulphur dioxide	200	520	1	20	52	10	26
114	Sulphur monochloride (S_2Cl_2)	20	112	1	10	56	5	28
115	Sulphuryl chloride	10	56	1	4	22	1	5·6
116	Tetrachlorethane	50	350	60	20	140	10	70
—	Tetrachloroethylene (Perchloroethylene)	See No. 106 Perchloroethylene.						
117	Thionyl chloride	20	100	1	10	50	5	25
118	Thiophosphoryl trichloride	10	70	1	4	28	1	7
119	Trichloroethylene	2,000	10,940	60	800	4,376	400	2,188
120	Toluene (Toluol)	1,000	3,830	60	300	1,149	100	383
121	(*o*, *m*, & *p*) Toluidines	40	176	60	10	44	5	22
122	Vinyl chloride	3,000	7,800	60	1,500	3,900	500	1,300
123	Xylenes (Xylols)	1,000	4,410	60	300	1,323	100	441
124	Xylidines	40	200	60	10	50	5	25
	Dusts, Fumes, and Metals							
125	Antimony (dust or salts) (as Sb)	—	—	—	—	—	—	0·5
126	Arsenious oxide	—	—	—	—	—	—	0·5
127	Barium salts (as Ba)	—	—	—	—	—	—	0·5

Concentrations shown in italic are tentative and are issued as a guide. Figures in all columns will be subject to review as more data become available.

* 1 mg./cu. metre ≡ 4·37 x 10^{-4} grains/cu. ft.

Continued

Table 1 continued

No.	Gas	(1) Concentrations Causing Severe Toxic Effects in Persons Exposed for the Stated Times			(2) Concentrations which, if Exposure Continues for more than a Short Time, may Lead to Symptoms of Illness		(3) *Concentrations in General Atmosphere of Plant Greater than those below Indicate Unsatisfactory Conditions*	
		(p.p.m. v-v)	(mg./cu.* metre 20°C.)	Time of Exposure (Min.)	(p.p.m. v-v)	(mg./cu.* metre 20°C.)	(p.p.m. v-v)	(mg./cu.* metre 20°C.)
128	Benzidine	—	—	—	—	—	—	*0·01?*
129	Cadmium	—	—	—	—	—	—	*0·1*
130	Chlorinated diphenyl	—	—	—	—	—	—	*1*
131	Chlorinated naphthalenes	—	—	—	—	—	—	*1*
132	Chromates (as CrO_3)	—	—	—	—	—	—	*0·1*
133	Dinitrocresol (and salts)	—	—	—	—	—	—	*0·5*
134	Dinitrophenol (and salts)	—	—	—	—	—	—	*1*
135	Dinitroresorcinol	—	—	—	—	—	—	*1*
136	Dinitrotoluene	—	—	—	—	—	—	*1·5*
137	"Dowtherm A"	—	—	—	—	—	—	*?*
138	Lead (and salts)	—	—	—	—	—	—	*0·15*
139	Mercury	—	—	—	—	—	—	*0·1*
140	α-Naphthylamine	—	—	—	—	—	—	*0·01*
141	β-Naphthylamine	—	—	—	—	—	—	*0·01*
142	"Parathion"	—	—	—	—	—	—	*1*
143	Pentachlorphenol	—	—	—	—	—	—	*0·5*
144	*p*-Phenylene diamine	—	—	—	—	—	—	*0·1*
145	Phosphorus pentachloride	—	—	—	—	—	—	*1*
146	Potassium permanganate	—	—	—	—	—	—	*?*
147	Sulphuric acid	—	—	—	—	—	—	*1*
148	Sodium cyanide	—	—	—	—	—	—	*5*
149	Tetryl	—	—	—	—	—	—	*1·5*
150	T.N.T.	—	—	—	—	—	—	*?*
151	Zinc oxide	—	—	—	—	—	—	*10*

Concentrations shown in italic are tentative and are issued as a guide. Figures in all columns will be subject to review as more data become available.

*1 mg./cu. metre = $4·37 \times 10^{-4}$ grains/cu. ft.

Changes in respiration and the respiratory system are usually secondary to irritation of the respiratory tract, to changes in blood pigment, to central depression, and to direct damage of the alveolar network. Less direct effects are produced by cholinesterase inhibitors, which lead to powerful parasympathetic stimulation, and by inhibitors of oxidative enzymes. The asthma-like attacks induced by some aromatic diamines and di-isocyanates are reversible.

It is unusual for the lungs to be the seat of transformation of compounds. But in the case of ethylene oxide, which has a wide application in the present-day chemical industry and in the fumigation of food, combination with water in the lung can yield toxic glycols which may easily have long-term effects.

Delayed effects on the lung itself (oedema, haemorrhage, emphysema) can be foreseen by animal experiment. Recent investigation in my laboratories of the notorious "nitrous fumes", which have been responsible for many deaths from pulmonary oedema, shows that the potent agent is N_2O_3, and that N_2O_4 is much less toxic as is also nitric acid vapour (Diggle and Gage, 1954).

Any toxic dust is injurious to the lungs although the pneumoconioses, and in particular silicosis, are our most serious and extensive industrial pulmonary diseases.

Fig. 1 shows a section of a lung of a rat which, with a group of other rats, was exposed for eight hours a day for many months to an atmosphere of 2 mg./cm. K_2CrO_4 as a very fine dust. The animals were well enough: there was a period of coughing and harsh breathing, but nothing serious. They lived on in quietude and sustained the chromate with bored fortitude but the lung shows large and small areas of exsanguinated alveoli crammed with loaded histiocytes in various stages of degeneration. Functionally these areas are out of action. The cell debris in the alveoli contributes further to loss of function until disposed of. Dilated respiratory bronchioles and some emphysema, due partly to the injurious effect of the chromate on the alveolar septa, and partly as compensation to the loaded alveoli, are also seen.

Fig. 2 is a high-power picture of a portion of a guinea-pig's lung after exposure for months to a very high concentration of lead acetate (40–50 mg./cm.). The origin of the dust cells from the alveolar septal cells is clearly seen, but monocytic cells undergoing hypertrophy from the capillary blood appear also to be passing into the alveoli.

FIG. 2.—Guinea-pig
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	(5) Concentrations in General Atmosphere of Plant Greater than those below Indicate Unsatisfactory Conditions	
	(p.p.m. v/v)	(mg. cu.* metre 20°C.)
	—	0·013
	—	0·1
	—	1
	—	1
	—	0·1
	—	0·5
	—	1
	—	1
	—	1·5
	—	2
	—	0·15
	—	0·1
	—	0·01
	—	0·01
	—	1
	—	0·1
	—	0·1
	—	1
	—	1
	—	1
	—	3
	—	1·5
	—	2
	—	10

* subject to review as more data

ive industrial pulmonary

f a lung of a rat which, , was exposed for eight ths to an atmosphere of y fine dust. The animals a period of coughing and g serious. They lived on ne chromate with bored s large and small areas crammed with loaded ages of degeneration. e out of action. The cell ibutes further to loss of Dilated respiratory bron- ema, due partly to the ate on the alveolar septa, n to the loaded alveoli,

ncture of a portion of a posure for months to a of lead acetate (40–50 ne dust cells from the seen, but mono- from the capillary passing into the alveoli.

FIG. 2.—Guinea-pig lung after chronic inhalation of fine lead acetate dust—origin of mononuclear phagocytes from blood and alveolar walls. Active phagocytosis seen both in the wall and in the lumen of the alveoli and coarse granular pigmented material in the phagocytes. × 300.

FIG. 1.—Rat lung after chronic exposure to fine potassium chromate dust: many areas of exsanguinated, functionless alveoli filled with [illegible] phagocytes and many ruptured alveoli. × 100.

FIG. 2a.—Phagocytosis of blood phagocytes by macrophages deriving from septal cells; details of coarse pigment granules in guinea-pig lung. 1200.

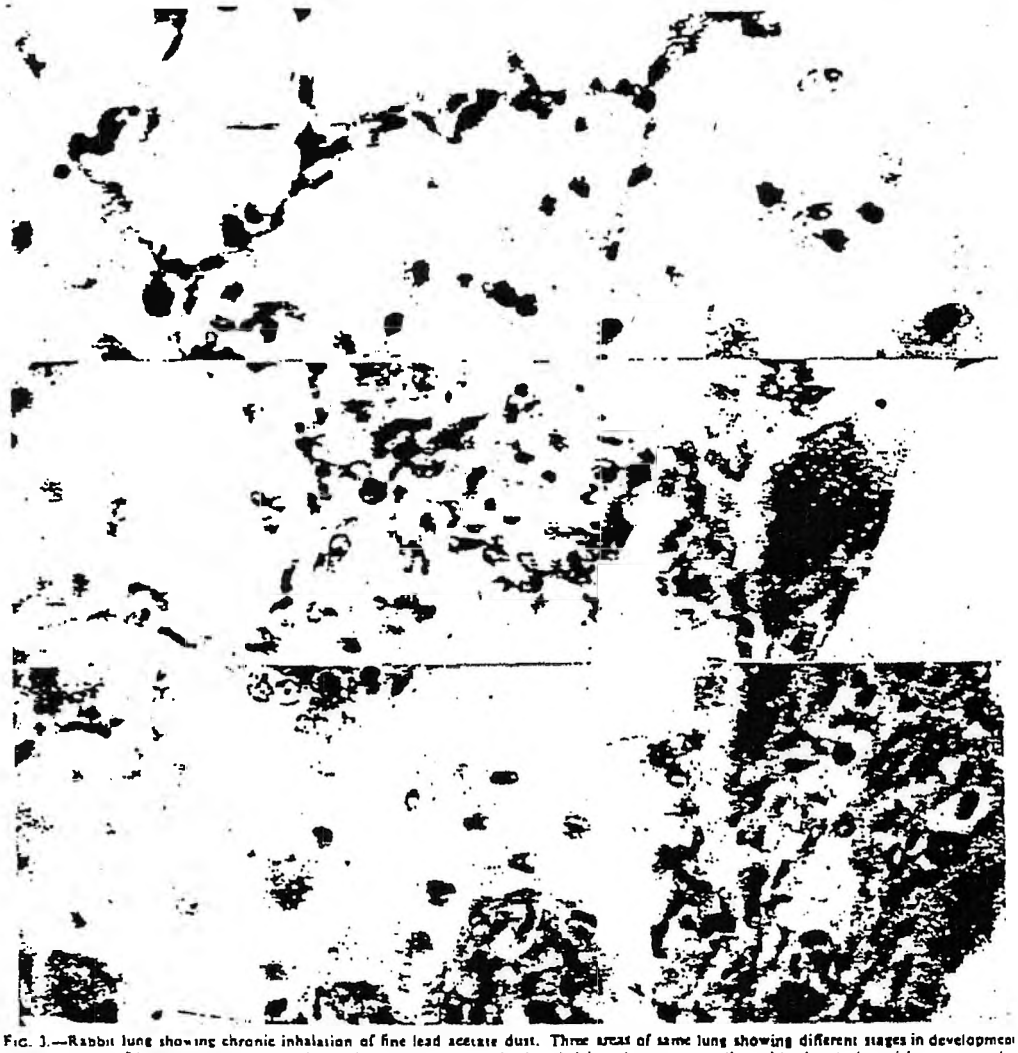

FIG. 3.—Rabbit lung showing chronic inhalation of fine lead acetate dust. Three areas of same lung showing different stages in development and death of lung phagocytes; small alveolus crammed with dead and dying phagocytes swollen with absorbed particles; note multinuclear macrophage. ×560.

These cells are later engulfed by the macrophages developed from the septal cells after having acted as dust cells themselves. The macrophages are seen to contain dark pigmented granules and nuclei in various stages of degeneration (Fig. 2a). In Fig. 2a the extent of phagocytic activity is striking. In Fig. 3 we see the progressive changes from the well stained cell in the alveolar wall to the dead dust cells in the alveolar spaces.

The effectiveness of the lung barrier to a toxic dust must depend upon the availability of phagocytes to act as a brake on absorption. At so high a concentration as that used in these experiments blood cells evidently enter as an additional defence. The barrier to dusts presented by the lung is paid for in the case of toxic dusts by a denudation of the precursors of the so-called dust cells (*i.e.* modified septal cells) and in oxygen capacity by the occupation of alveolar spaces by highly charged cells and cell debris when the toxic material is discharged. The formation of giant multinucleate cells also occurs in the chronic inhalation of toxic dust (Fig. 3). In a universe of dust processes of this kind are inevitable but it is our business to combat industrial dust with other weapons than our lungs.

Changes in blood pigments are mainly found in industry among those exposed to carbon monoxide, various aromatic nitro- and amino-compounds, and

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metallic elements which interfere with haemoglobin formation. These effects cannot all be demonstrated with equal ease in all species of laboratory animals.

The deliberate induction of methaemoglobinaemia in the treatment of cyanide poisoning is of practical importance, and recovery in very severe cases has been obtained by Lloyd Potter (1950). The method depends upon the intravenous injection of sodium nitrite which, by forming methaemoglobin, permits the circulating cyanide to react to form the much less toxic cyanmethaemoglobin and upon the intravenous injection of sodium thiosulphate which accelerates the formation of thiocyanate from the now slowly liberated cyanide.

Renal and hepatic function can be affected by many chemical agents ; among these are certain industrial metallic poisons, organic solvents, notably chlorinated aliphatic hydrocarbons, explosives, derivatives of glycols. Reversibility in these cases is endangered for the change-over from dysfunction to structural breakdown is poised precariously. The peculiar position of trichloroethylene among the commonly used solvents, however, indicates how subtle must be the mechanism which determines its low toxicity, which is perhaps related to its ready metabolism to the non-toxic trichloroacetic acid (Taylor, 1936 ; Powell, 1945).

For certain metabolic aspects of toxicity and carcinogenicity the use of isotopes is assuming wider and wider significance. A bladder carcinogen with one carbon C^{14} has recently been prepared by members of my department in collaboration with Amersham (Henson, 1953 ; Catch, Huggill, and Somerville, 1953). We have already been able to establish important metabolic pathways and the long retention of compounds carrying the labelled atom in the body (Henson, Somerville, Farquharson, and Goldblatt, 1954). The detection of the location of toxic compounds in cells by autoradioactivity in histological sections is already a developing method.

The ultimate fate of most materials absorbed in industrial conditions is unknown. A great deal is known about some of the final forms in which many chemical substances are disposed of in animals, but we are very rarely able to strike a balance by ordinary or even extraordinary chemical means. The subtle ways in which complex substances introduced into the body in large part "disappear" raise many difficulties and apprehensions. Nevertheless, by using labelled compounds a new era has been opened in obtaining almost complete balance between intake and output of substances containing isotopic atoms, and in discovering how long such substances or their derivatives are retained in the body. In addition it is possible to track them through the various routes they can take in the body and, if retained for long periods, to learn where they are deposited.

Industrial metabolic poisons interfering with phosphorylating processes are dinitroorthocresol (D.N.O.C.), dinitrophenol (D.N.P.), and pentachlorphenol, the former two being responsible for both clinical and industrial deaths, and the latter for recent industrial deaths. Dinitro aromatic compounds require careful study as some may induce cataract. Indirect metabolic effects may arise from interference with normal thyroid function as in the case of some alkyl-nitro-amino derivatives of phenol.

The haematopoietic system is one of the first examined in the case of most industrial chemical hazards with chronic effects. Blood counts are sometimes undertaken on workers in many different branches of the chemical industry, especially where hydrocarbon and chlorinated hydrocarbon solvents, explosives, some metals, radioactive materials, and many other materials are made or used. Animal experiment often gives the appropriate lead as to the nature of the attack on the blood-forming organs or on the blood itself, although there are difficulties from the much greater variability of the blood picture in animals than in man. Reversibility of effects on the blood depends upon removal of the noxa and on the functional recovery of the bone marrow.

Clinical and Experimental Aspects of Lead Intoxication

Much has been done to elucidate the clinical picture and pathological processes of lead intoxication and poisoning. As the result of 12 years' experience of men in a factory where lead acetate, lead pigments, and paints were manufactured certain clinical and elementary propositions have been formulated. The first is that the control of the health of workers exposed to any lead hazard is easy and effective by routine determination of (*a*) haemoglobin, and (*b*) stipple and polychromatic red cells. More complex methods are required in certain of the more highly dangerous lead hazards, *e.g.*, volatile organic lead compounds.

The expertise to do this is minimal, and a junior boy or girl can be trained to do it and even interpret the findings in a short time. If the conventional method by transmitted light be used, then it should be realized that the polychromatic cell is a stipple cell with the stipples very closely set, and they should be counted together, and can readily be confirmed by dark-ground examination (Figs. 4 and 5).

Haemoglobin determination alone is not sufficient, for many patients are found with 100 to 90% haemoglobin who may be presumed to be absorbing lead from the high (stipple and polychrome) counts. Nor

FIG. 4.—Rabbit blood stained with alkaline methylene blue and photographed by transmitted light showing various-sized basophilic (polychromatic) cells due to chronic lead exposure.

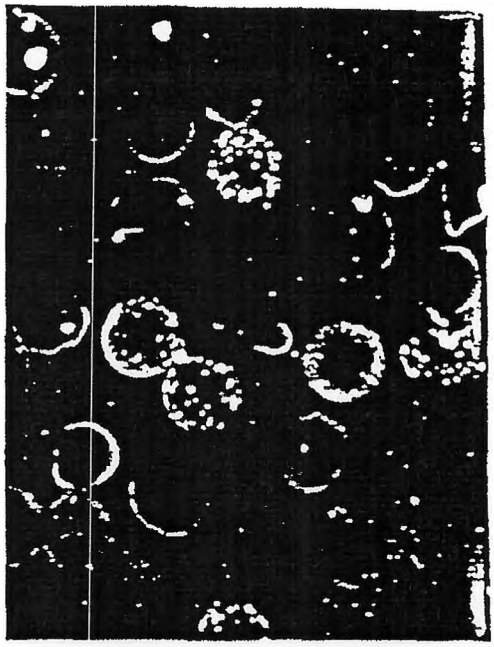


FIG. 5.—Rabbit blood stained with alkaline methylene blue and photographed by dark ground illumination showing ease of recognizing stipples (golden granules) and two polychromatic cells: the polychromatic cells are manifestly very finely stippled cells.

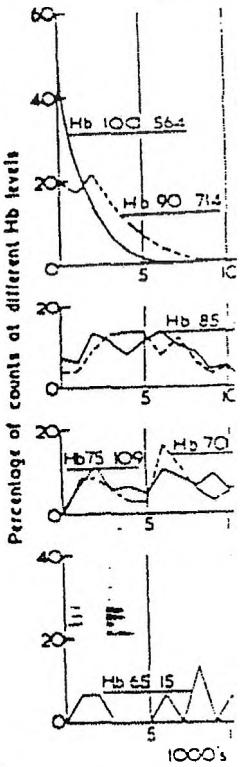


FIG. 6.—Relation between haem in workers exposed to a examined shown with Hb

is the stipple and polychromatic count sufficient, for a relatively low count is frequently found with a very low haemoglobin (Fig. 6).

The second proposition is that it is not difficult to prevent the notification of cases of lead poisoning by removing men from exposure at a critical moment and giving them other work. This is, in fact, what happens in most factories with a hazard from lead.

Since in most cases rapid recovery is the rule, the statistics of lead intoxication can be kept low, and the national returns become valueless as far as a national industrial picture of lead absorption is concerned. Moreover, men kept on at work in spite of evidence of lead intoxication do not develop a proper respect for lead and hence develop recurrent attacks of lead poisoning (see also Fullerton, 1952) (Table 2). As a rule (this is my third proposition) no man at work makes as good or as quick a recovery from lead intoxication as he does at home or in hospital (Table 3), so the importunities of men to be kept at work in spite of evident lead intoxication should be resisted and they should not be allowed to return to work until the normal blood picture is re-established. The recent introduction of chelating agents may expedite recovery and return to work (Foreman, Hardy, Shipman, and Belknap, 1953).

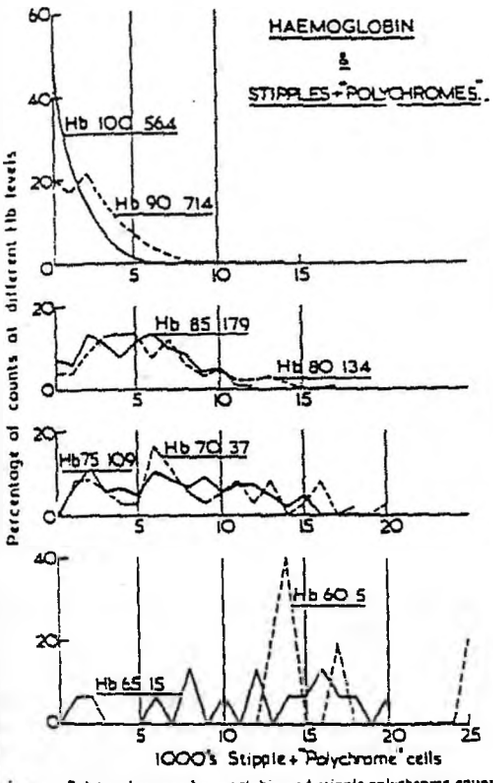
Kehoe (1951) has emphasized that the usual forms of lead intoxication are self-limited, of relatively short duration, and that there is complete recovery when the exposure has been terminated, and that no irreversible damage to the blood-forming tissues is associated with plumbism. The cases to which this statement would not apply are the now exceedingly rare encephalopathies and muscle palsies.

Fig. 7 shows the kind of picture one would wish to avoid, that of a man who took five years to recover his haemoglobin although removed from contact with lead (see also Fullerton, 1952).

Fig. 8 shows the data on a case of some interest. Three months of work on lead were followed by a fairly acute episode from which the patient was allowed to recover while still at the factory doing odd jobs not involving contact with lead. In spite of a very big drop in the number of stipples and polychrome cells, the haemoglobin level recovered poorly. A subsequent period on work with lead again led to an episode which was certified. Certified as fit to work after 21 days, the patient was again

Year	No.	Name	Tir Ls
1950	1	F.G.	
	2	W.P.	5
	3	G.F.K.	10
	4	J.S.	2
1951	5	S.F.	26
	6	K.A.M.	11
	7	A.W.	16
	8	P.N.	2
			0
1953	9	T.H.	13
			13
1955	10	E.M.	23
	11	F.H.W.	1
			2

with alkaline methylene blue and illumination showing ease of granules) and two polychromatic cells are manifestly very finely



—Relation between haemoglobin and stipple-polychrome counts in workers exposed to a lead dust hazard. Numbers of bloods examined shown with Hb values. (See text).

turn to work (Foreman, snap, 1953).

sized that the usual forms self-limited, of relatively here is complete recovery n terminated, and that no e blood-forming tissues is . The cases to which this y are the now exceedingly muscle palsies.

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n a case of some interest, lead were followed by a n which the patient was still at the factory doing ontact with lead. In spite e number of stipples and emoglobin level recovered on work with lead as *certified*. Certi- , the patient was again

maintained in the factory on work involving no contact with lead till the haemoglobin was about 85%. A period on lead again threatened an episode, and subsequently a change to permanent work elsewhere led to a slow and unsatisfactory recovery to almost 90% haemoglobin in about two years.

Finally, it is important to remember that there are men who are remarkably reactive to even small amounts of lead. This is seen well in Fig. 9 which shows the blood findings in a worker who reacted at once when given work on a lead process, showed great falls in haemoglobin without a simultaneous rise in stipples, and who oscillated violently even when on work not involving a lead hazard. Lane (*loc. cit.*) and others have described cases of hypersensitivity and referred to evidence of family susceptibility to lead. A full study of such cases would be of considerable interest. The influence of alcohol must not be forgotten.

My fourth proposition is that the changes in the peripheral blood in lead intoxication are due to changes in the bone marrow.

The stippled red cell derives from stipple normoblasts in the marrow, both of which may be seen in the circulating blood (Figs. 10 and 11). The stipples of a normoblast in the bone marrow are seen as a corona round the nucleus for mitosis occurs in the stippled normoblast apparently normally.

There are far more stipple cells in the bone marrow per million erythrocytes than in the circulating blood during lead intoxication. Pirrie (1952), using guinea-pigs, found as many as 55% of haemoglobinating normoblasts in the marrow showing basophil stippling when only 2·5% of red blood cells were

TABLE 2

LOST TIME OF TWO GROUPS

Certified*								Uncertified†							
Year	No.	Name	Time Lost	Year	No.	Name	Time Lost	Year	No.	Name	Time Lost	Year	No.	Name	Time Lost
1939				*1940*				*1936*				*1939*			
	1	F.G.			12	W.C.	3 days	28 : 10	1	*E.E.*	Nil	23 : 1	16	*C.F.H.*	Nil
	2	W.P.	8 days		13	A.H.T.	1 mth.	9 : 12	2	*E.E.*	Nil		17	A.E.P.	20 days'
	3	G.F.K.	10 days				13 days	4 : 11	3	*W.F.*	Nil				investigation
	4	J.S.	2 mths.	*1941*	—	—	—		4	*F.G.*	Nil		18	A.W.	Nil
1940								14 : 10	5	*F.K.*	Nil	*1940*			
	5	S.F.	26 days	*1942*	—	—	—	28 : 10	6	*F.K.*	Nil	23 : 9	19	*H.J.*	Nil
	6	K.A.M.	15 days	*1943*					7	H.E.W.	3 days		20	G.M.	Nil
	7	A.W.	16 days	20 : 11	14	*G.F.M.‡*	1 mth.			(Hb. 75 %)	gastritis	*1941*	—	—	—
	8	P.N.	2 mths.				4 days	*1937*							
			6 days					24 : 1	8	*W.F.*	Nil	*1942*	—	—	—
1938				*1944*				5 : 5	9	*W.F.*	Nil				
	9	T.H.	11 days	17 : 4	15	*G.F.M.*	30 days		10	*F.G.*	Nil	*1943*			
			18 days						11	C.J.H.	Nil	22 : 5	21	*H.J.*	Nil
1939									12	J.L.	Nil				
	10	E.M.	28 days						13	R.O.	Nil	*1944*	—	—	—
	11	F.H.W.	1 mth.					*1938*							
			21 days					13 : 12	14	*C.F.H.*	Nil	*1944*			
									15	W.R.	Nil	26 : 1	22	*H.J.*	

*Certified = recovery away from factory. †Uncertified = recovery at work.
(All cases 60–65 % Hb at time of certification or action in factory.) ‡Recurrent cases in italics.

TABLE 3

PERIOD OF RECOVERY OF Hb

	Maintained at Work	Removed to Home or Hospital
Cases	24	9
at time of sfer	65–70%	65–70%
ume to reach or more	1·93 months (3 weeks–7½ months)	1·66 months (16 days–2½ months)

dicates slight advantage of getting man away from factory even ght and non-lead work.

case of Hb 45–45% recovered to 80% in 28 days whilst at work non-lead.

ppled in the stained peripheral blood. Similar dings were obtained in our experiments with bbits. Even in heavy exposure to lead not all the ormoblasts show stipples, many proceeding to ormal haemoglobination. Stipple cells, poly-hromatic cells, and reticulocytes all owe the ppearances seen to ribonucleic acid. This can be hown by treating the cells with ribonuclease which ompletely removes the basophilic material and leaves the cells uniformly acidophil. In the normal maturation of the erythrocyte, the basophilic substance in the cytoplasm practically disappears at the reticulocyte stage, and haemoglobination is completed without a hitch.

The delivery of "leaded" basophilic cells from the marrow into the circulation is gradual in ordinary circumstances as the peripheral cells are removed. This statement applies to reticulocytes, polychromatic cells, and stipple cells, and it must be clearly understood that the particular appearance associated with these cells is not preformed, but depends upon the method of staining and upon the amount and state of the basophilic substance. Conditions suitable for staining one kind of these cells may fail entirely for the others.

If blood rich in reticulocytes is stained supravitally with brilliant cresyl blue the usual picture is obtained of a filamentous-granular network but if a dried film is stained with the same dye the reticulocytes are seen as cells with vacuolated basophilic material (Figs. 12 and 13). Stained supravitally or in dried film stipples are readily seen in their usual form in red blood cells as well as in normoblasts. Reticulocytes stained in dried film and examined in the dark ground show a finely granular or finely reticular pattern with irregular vacuoles.

MacFadzean and Davis (1949), Pirrie (*loc. cit.*), Rimington (1938), Kench, ane, and Varley (1952), Dustin (1942), and others have gone far to elucidate the nature of the stippling property of the erythrocyte in lead absorption.

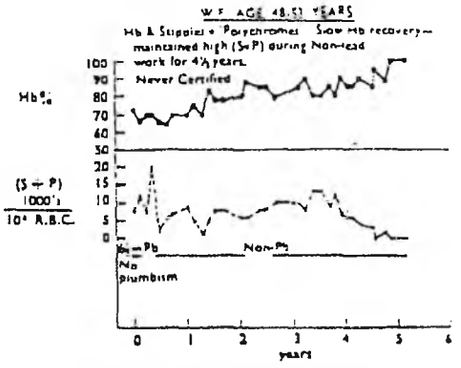

FIG. 7.—Case of lead anaemia showing extremely slow recovery of haemoglobin whilst maintained at work.

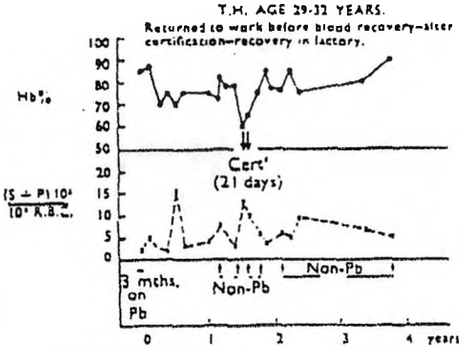

FIG. 8.—Case of certified plumbism considered clinically fit to return to work, but thereafter requiring almost two years to regain a stable Hb on non-lead work.

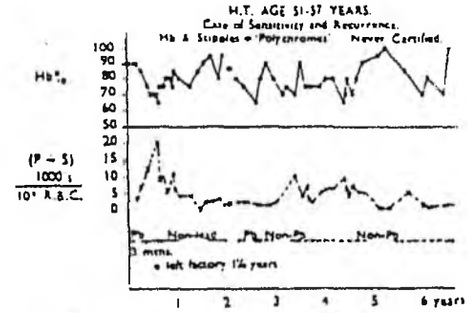

FIG. 9.—Case of sensitivity and recurrent lead anaemia in spite of long periods on non-lead work. Close correspondence of Hb and stipple values.

Lead poisons the later precursors of the red cell and intoxication manifests itself as (1) retention of basophilic material instead of its almost complete disappearance at the normoblast and reticulocyte stage and completion of maturation. (2) The so-called stipple cell and the polychromatic cell derive from the failure of maturation of the basophil normoblast. The reticulocyte derives from non-poisoned normoblasts. Since reticulocytes may increase before lead anaemia and stippling are established we may assume that the stipple and polychrome cells indicate a failure of the normoblast to go on to the reticulocyte stage. With the failure of the bone marrow in extreme cases of lead poisoning, stipples, polychromes, and reticulocytes all fail. This is why stipple counts fall in the last stages of very severe lead poisoning. (3) By processes not properly understood (synthesis of porphyrin, incorporation of Fe into coporphyrin III to form haemoglobin, etc.) lead inhibits the full haemoglobination of red cells. (4) Evidence of abnormality of red cells in lead absorption is that they show (*a*) diminished fragility in being able to withstand lower salt concentrations ; (*b*) increased brittleness and less durability in the conditions of existence in the circulation. In addition, they are readily taken up and destroyed by the spleen and other reticulo-endothelial cell locations. (5) Lead anaemia is due to (*a*) poor haemoglobination and (*b*) greater destructibility of cells containing lead.

Industrial Enzyme Poisons

Many industrial poisons are enzyme inhibitors, *e.g.*, cyanide, organic arsenicals, organo-phosphorus compounds. The clinical pictures of acute poisoning can sometimes be related more or less specifically to the inhibition of particular enzyme systems.

The most important of these has, in recent years, been the large group of organic phosphorus insecticides (Fig. 14) and potential war gases. Since there is intense competition in this field of manufacture, chemical research is directed towards synthesizing compounds which combine a broad spectrum of high insecticidal activity with low mammalian toxicity.

The toxicity of these compounds (Table 4) is attributable to their inhibition of cholinesterase and hence the clinical picture of poisoning is that of poisoning by endogenously produced acetylcholine. But the degree to which they inhibit the enzyme *in vitro* is in some cases many (even millions of) times less than would be expected from their toxicity *in vivo*. Transformation into highly potent anti-cholinesterases occurs in these cases in the liver.

Recently progress has been made towards evolving organo-phosphorus compounds possessing low mammalian toxicity compared with the now classical

TABLE 4

L.D.50. ORGANO-PHOSPHATE INSECTICIDES*

Compound	Oral L.D.50	I.P. L.D.50
T.E.P.P.	1·2 R.f. 2·0 R.m.	0·65 R.
Paraoxon	3·5 R.m.f.	1·2 R.m.f.
Dimefox	5 R.m.	
Systox (Commercial) ..	6·39–9·3 R.m.	4·5–8·37 R.m.
S || >P–O–	7·5 R.m.	
O || >P–S–	15 R.m.	
Pestox (O.M.P.A. Schradan)	9·7–10·0 R.m.f.	8·0–8·5 R.m.f.
Parathion	6 R.f. 15 R.m.	4 R.f. 7 R.m.
E.P.N.	14·5 R.f. 91·0 R.m.	50 M.
Mipafox	< ⅓₀ Parathion	
Malathion	2,420 R.f. 2,860 R.m.	750 R.

*Median lethal doses of organo-phosphate insecticides. R = rats, M = mice, m = male, f = female. All values in mg./Kg.

parathion and tetraethyl pyrophosphate (T.E.P.P.). Thus "mipafox", which is the mono-isopropyl analogue of "dimefox", is perhaps 25 times less toxic than "parathion", and "malathion" about 200 times less toxic to mammals. The optimism engendered by these facts is tempered in the case of "malathion" by its less potent insecticidal properties and in that of "mipafox" by pathological considerations.

The questions which must be answered by the industrial investigator in respect of these and other agents which are applied to food or crops are : (1) Do they constitute a risk to the consumer of the food products? This has been adequately answered in the report of the working party appointed by the Ministry of Agriculture (1953) which gives the necessary assurance but recommends investigation of the maximum permissible residues arising from the use of toxic substances. (2) Do they constitute an unjustifiable risk to the user? The answer here is no, provided that the necessary precautions are implemented, and, in addition, if the use of atropine is properly understood by employer, supervisor, and doctor as the specific therapeutic agent for the parasympathetic signs and symptoms (Goldblatt, 1950, 1951).

The onset of symptoms depends upon the level of true cholinesterase in the blood cells, brain, and nervous tissues, in nerve fibres and at motor end-plates and, of course, at ganglionic synapses. Since a great fall in the enzyme may occur in some individuals without any manifest signs or symptoms, it is essential that the blood cell cholinesterase of exposed persons should be determined as a routine

ICIDES*

I.P. L.D.50
0·65 R
1·2 R.m.f.
4·5–8·37 R.m.
8·0–8·5 R.m.f.
4 R.f.
7 R.m.
50 M.
750 R.

insecticides.
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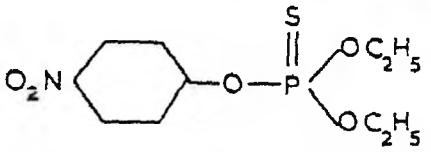
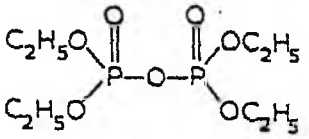
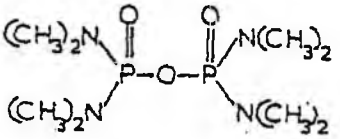
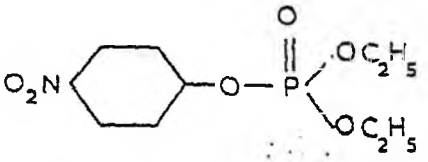
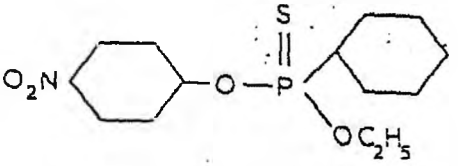
ORGANO–PHOSPHORUS INSECTICIDES

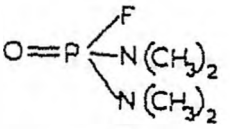
1). PARATHION 

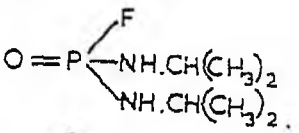
2). T.E.P.P. 

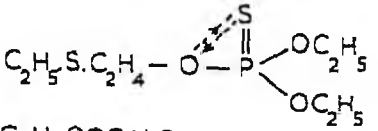
3). PESTOX 

4). PARAOXON 

5). E.P.N. (U.S.A.) 

6) DIMEFOX  SYSTEMIC

7). MIPAFOX  SYSTEMIC

8). SYSTOX  SYSTEMIC

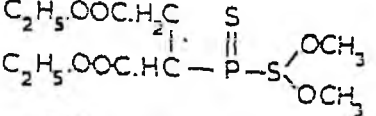
9) MALATHION  LEAST TOXIC

FIG. 14.—Formulae of active compounds in organo-phosphorus insecticides.

in order to preclude a fall to dangerous levels ; each subject should be his or her own control. The variance from mean levels in populations is too great to draw conclusions from single observations. It is so easy to ignore the early symptoms which may be no more than a slight tightness in the chest and a sense of mild apprehension. This is the more important since in irreversible inhibition of cholinesterase there is considerable delay before the normal enzyme level is regenerated. In the case of "mipafox" poisoning it may take 50 to 90 days to recover the initial red blood cell level of cholinesterase after an acute severe attack.

Until very recently it would have been held that the organo-phosphorus insecticides did not produce chronic effects, acute non-lethal attacks passing off without sequelae and long-term administration of sub-lethal doses to animals giving rise to no chronic toxic phenomena. Clinical observation and experiments had shown that among organo-phosphorus compounds D.F.P. (di-isopropyl-phosphorofluoridate) and T.O.C.P. (tri-*o*-cresyl phosphate) both in man and in animals could induce demyelination in the cord and in the brain, and although suspicion was cast, by analogy, on the phosphorous insecticides, it was not till 1951 that a case of paralysis due to "parathion" was described in Germany by Petry (1951) and two cases due to "mipafox" (bis-(mono-isopropyl) phosphorodiamidic fluoride) in this country by Bidstrup, Bonnell, and Beckett (1953), none of which appears to have recovered in some three years.

The addition of these agents to the already known diversity of demyelinating agents in man and animals (carbon monoxide, arsenicals, sulphanilamide, spinal anaesthetics, vaccination) tends to turn us from a purely chemical hypothesis to perhaps an enzymatic one. Demyelination has been produced experimentally with CO, KCN, N_3Na, N_2O, and repeated doses of barbiturates (Weston Hurst, 1941, 1944).

The paralysis which followed "parathion" and "mipafox" resembled that described among many people who had absorbed T.O.C.P. in one way or another, and in both these groups it seems probable that the persistent signs were due to demyelination.

Fig. 15 shows a section of the cord of a fowl (1·35 kg.) treated with a single dose of 0·5 g./kg. of tri-*o*-cresyl phosphate (T.O.C.P.). This and another fowl similarly treated were observed for over 250 days. The phenomena were of the same kind as found with the anti-cholinesterase insecticides. Some recovery was observed, especially in respect of secondary sex characters and egg-laying power, and to some extent in muscular powers, but this was very slow and only partial (see also Barnes and Denz, 1953).

The selection of a special tract for attack is puzzling and not less so than in man, in whom the whole picture is of a motor disturbance. In the cases due to insecticide a neuromuscular block due to the breakdown of the normal relation of cholinesterases and their substrates was first seen and later a peripheral neuritis with only those sensory impairments as are normally associated with polyneuritis.

As more and more compounds are being synthesized, it is important not to assume the relative safety of a given compound until acute and chronic

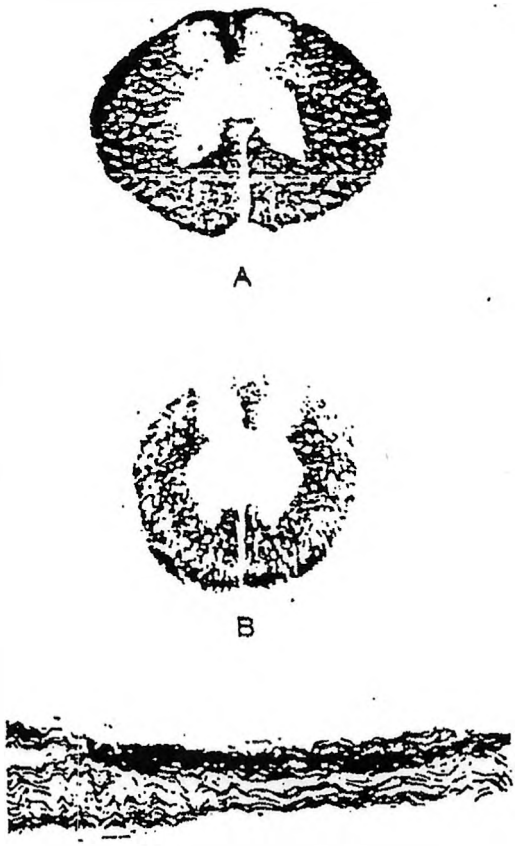


FIG. 15.—Cervical cord and sciatic nerve of a fowl treated with a preparation of tricresyl phosphate calculated to contain 0·1% of the ortho-isomer. Total dose in 16 days = 2 mg./kg. by mouth. First paralytic signs in 21 days followed by progressive worsening of paralysis of legs. Demyelination in anterior and lateral columns and markedly on sciatic cord. × 12. Marchi's method. A = upper, and B = lower, cervical cord -below sciatic nerve.

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experiments have been carried out, and also the effect on the nervous system studied in detail in a variety of animal species.

Occupational Carcinogenesis

There are very few identifiable agencies which have been shown without any doubt to be carcinogens to man. These are arsenical compounds, radiations (x-ray, radium, ultra-violet light), β-naphthylamine, benzidine, and probably 3·4 benzpyrene.

Of the host of compounds and complex mixtures which have produced tumours of skin, liver, mammary gland, lung, and bladder in animals, only these have been demonstrated as direct or indirect human carcinogens. The active agents in such carcinogenic products as tar, lubricating oil, soot, pitch, are not established with certainty, although the isolation of 3·4 benzpyrene from tar casts strong suspicion on this compound.

Long-continued therapy with arsenical preparations and work with arsenical compounds have led to indubitable skin changes (hyperkeratosis) and finally to epitheliomata. But no convincing experiment has been published to demonstrate a similar effect in animals.

In the case of certain radiations, neoplastic change as well as severe blood changes have undoubtedly followed long exposure in man and in animals, though the tumours which develop are different—sarcomata in animals and carcinomata in man. The differences are attributable to the different tissues reached by the radiation.

Neoplastic changes, sometimes benign but most often highly malignant and recurrent, in the bladders of workers exposed for varying periods to the fume and or dust of certain aromatic amines have been reported for nearly 60 years in all parts of the world where organic dyestuffs are manufactured. This clinical fact has been confirmed by experiment both in the U.S.A. and in Britain with dogs in which identical bladder tumours were induced by feeding β-naphthylamine. It has been suggested by Bonser, Clayson, and Jull (1951) that the incidence of bladder tumours inducible by treatment with β-naphthylamine in different species is roughly related to the amount of urinary conjugates of 2-amino-1-naphthol excreted.

More recently the same suspicion fell upon benzidine and has been amply confirmed. Intensive research both inside and outside industry has led to the demonstration of the carcinogenic properties of benzidine in rats (rectum, sebaceous ear glands, liver) but bladder tumours had until recently not been induced except in the case of one dog (Spitz, Maguigan, and Dobriner, 1950). The possibility that here also the *o*-hydroxyamine is the immediate carcinogen has received much consideration.

The contribution made to the elucidation of the problem in this country has been notable and the names of Bridge (1934), Macalpine (1929,) Wignall (1929), Walpole, Williams, and Roberts (1954), Scott (1952), Baker (1953), Bonser and others, (1951), Bonser, Clayson, Jull, and Pyrah (1952) and more recently Case and Hosker (1954), and Case, Hosker, McDonald, and Pearson (1954), will always be remembered for the great light shed upon it. The total number of cases which Case and his colleagues (1954) were able to trace in the chemical industry between 1900 and 1952 was 455. Case's classical statistical investigations are a model for the future investigation of occupational diseases. Case and others have established on a national scale what others have found in industrial practice both in this country and elsewhere. Contact with the naphthylamines or benzidine is now fully recognized as a carcinogenic hazard, and aniline appears to be exonerated. Some as yet cryptic factors in the manufacture of magenta and auramine appear to throw suspicion on both these processes. The disease was prescribed as an industrial disease in 1953 in this country, just 58 years after the original description by Rehn. It is proper to record the unremitting clinical control by Dr. Charles Cresdee for almost a quarter of a century in one very large centre where these compounds were manufactured, which has been a guide and an inspiration to those who have had to pursue the problem in the quiet of the laboratory (for earlier work and review see Goldblatt, 1947, 1949).

More recently, arguing very ingeniously from the fact that these tumours had formerly been attributed to aniline, which until now has not been proven to be a bladder carcinogen, Walpole, Williams, and Roberts (1954) in Manchester came to suspect 4-amino diphenyl, which had been found in residues in aniline manufacture 80 years ago, as the probable cause. Experiments on dogs confirmed the presumed bladder carcinogenicity of this compound.

Certain condensation compounds of the naphthylamines formerly used in the processing of rubber have already been banned by manufacturers since new knowledge on the previously suspected but uninvestigated incidence of vesical tumours in the rubber industry became available (Case and Hosker, 1954).

Both the Leeds and Manchester workers have come to place great emphasis on *o*-hydroxyamines as the effective bladder carcinogens. This has opened a large speculative field of inquiry, because

a considerable number of hitherto unsuspected aromatic amines and derivatives of them could yield various o-hydroxyamines metabolically.

The dilemma before industry in this field is how to deal with the considerable numbers of compounds that might carry suspicion. The project of examining all the derivatives of cyclic hydrocarbons and their homologues which, in their metabolism, might yield amines or derivatives of amines of potential carcinogenicity must, however, be undertaken. There is no escape from the argument that if a compound is carcinogenic in animals, in whatever location in the body, it must be so regarded, at least potentially, in man. In some cases it is possible to circumvent carcinogenicity chemically. In the case of β-naphthylamine this has been done in this country and in some continental countries by avoiding liberation of the base at any stage of manufacture or use. Certain food azo-dyestuffs have already been rejected because of the possible metabolic fission of the relatively simple molecules with the liberation of a carcinogenic amine, in the absence of any but presumptive evidence. A systematic study of food colours on these lines is in progress in my laboratories.

In the industrial field the manner of attack must be cooperation between statisticians, industrial doctors, and experimentalists. The statistical weapon is one which is potent in the hands of specially gifted people, provided all the data are collected on a pre-determined plan and all in possession of relevant records cooperate fully. Before it is prudent to publish the view that a given material is not carcinogenic in any circumstances, it is well to remember that experienced investigators have made such statements and subsequently have been proved mistaken.

Experiment (in our hands as well as in others') has failed to show carcinogenic properties in chromates, but in the U.S.A. there is considerable statistical support that chromate dust can induce lung cancer (Machle and Gregorius, 1948) but Bidstrup (1951) was not able to draw clear conclusions from her x-ray survey of 724 workers in the industry in this country. Recent statistical data in the U.S.A. show that chromate workers had a mortality rate for respiratory cancer 29 times as great as would be expected among a comparable group of all males in the country (Federal Security Agency, 1953).

In 1949 the Senior Medical Inspector of Factories gave reasons for the belief that the pulmonary fibrosis in asbestosis is followed by an inordinately high percentage of cases of pulmonary cancer. It will be difficult, if the observation is confirmed, to envisage the process here as other than one initiated by local mechanical irritation but a chemical carcinogen is not ruled out although it is more difficult to find support for it. It is not sufficient to state that a given material is non-toxic. Toxicity as ordinarily understood is in some sense the reverse of carcinogenicity. For whereas a compound exercising a toxic effect on a cell is driving that cell in the direction of inanition and death, one exerting a carcinogenic effect on a normal cell is driving that cell towards excessive, if abnormal, function and, for a time, more vigorous life. This is not to say that a carcinogenic compound is never toxic in the ordinary sense, but rather that a toxic agent in full spate is unlikely to permit the establishment of carcinogenicity. Although the mean induction times for certain occupational carcinogens are long and not dependent on the severity of exposure, it is to be noted that in some individuals the induction time may be quite short and in others much longer than the mean.

Recent Work in the Diagnosis of Vesical Tumours

The need for continued medical supervision of men who have been exposed in the past to bladder carcinogens is manifest even after exposure has ceased, and even after leaving the industry.

In a section of the chemical industry exfoliative cytology is being used to detect early bladder tumours. In the U.S.A. the teaching of Papanicolaou (1947, 1948) on the importance of the recognition of neoplastic changes in exfoliated cells has been much regarded. Cells may be exfoliated from the lung, stomach, bladder, cervix, and vagina, and, provided the morphological and staining characters of tumour cells can be recognized, there is no theoretical reason why a neoplastic process should not be detectable at an early stage (see also Bamforth, 1953).

In the case of bladder tumours the early development is not attended by any disturbance of the patient in either occupational or non-occupational cases. Hence arises the need to establish routine urine examinations for microscopic blood, which is often the earliest sign of bladder irritation, of ruptured small varicosities, of a broken frond of a small papilloma, or of the slow and insidious oozing of an infiltrating carcinoma. In a small proportion of cases microscopic haematuria is unaccompanied by a tumour visible in the cystoscope, and in a larger proportion there may be no blood in spite of the presence of a tumour.

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cystoscopy of workers as it is practised on the Continent and to some extent in the U.S.A. Hence urinary examinations must be made and every device used which will, with the minimum discomfort, give a correct picture of the inside of the organ. To this end we are seeking to enlarge the scope of urinary examinations by determining the picture of vesical exfoliation in normal subjects, by applying Papanicolaou's methods to the urine, and, we hope later, by cytochemical tests for malignancy. By methods different from those hitherto used, Mr. Rofe in my laboratories has been able accurately to stain, characterize, separate, and count the types of cells found in normal human urine (Rofe, 1955) after removal of the normally interfering organic and inorganic matter and debris and concentrating the cells in 1 in 1,500 of the volume in which they were voided. Certain conclusions may thus be stated: (1) Most normal urines contain blood. (2) Most normal urines contain leucocytes. (3) The cellular content other than these is divisible into two main parts (*a*) squamous and transitional, 15μ and over in size (urethra, bladder); (*b*) small epithelial cells derived from kidney and prostate (in the male) 15 μ and under in size. These cells are in various stages of degeneration.

A very interesting feature of these results was that there were always far more leucocytes in normal urine than could be accounted for by a simple transudation of whole blood. This perhaps means that the bladder is always in a state of some irritation, either chemical or mechanical, which does not reach consciousness. By applying Rofe's method it is possible to see at a glance all the cells exfoliated in a given sample of urine. Having a reliable picture of the normal cell content, deviations from it can the more readily be recognized and the detection of exfoliated tumour cells is facilitated by the small volume into which the cells are concentrated. The character of exfoliated bladder tumour cells has been described by Crabbe

FIG. 16

FIG. 16.—Smear from urine of worker in manufacture of dyestuff intermediate, showing erythrocytes, polymorphs, abnormal and degenerated epithelial cells, and several definite malignant cells. Papanicolaou's technique of preparation and staining. × 500.

FIG. 17.—Smear from another dyestuff worker showing erythrocytes, many polymorphs, and giant binucleated malignant cells. Papanicolaou technique. × 500.

FIG. 17

(1952) working in my laboratories. The value of cytological diagnosis has been amply demonstrated.

The cytological criteria laid down by Papanicolaou for the diagnosis of malignancy include increased size and bizarre shapes; enlargement of nuclei in relation to cytoplasm; altered nuclear and chromatin pattern; increased affinity of nuclei for basic stains; and variation in nuclear sizes in a group of cells (Figs. 16, 17). In a method of diagnosis of this kind the danger is the false negative. The false positive is less serious, but always of great interest, especially when found in the absence of blood cells and cystoscopically visible tumours. The cystoscope is not infallible, for we have had cases in which a positive cytological diagnosis was subsequently confirmed by cystoscopy after initially negative cystoscopic reports.

It is becoming clear that the exfoliation of cells from new growths is not a uniformly constant process. One day it may be prolific, another relatively unproductive. Further, the ease of recognition of neoplastic character varies.

For these and other reasons we prefer at this stage to base judgment on a combination of the classical search for haematuria and to fortify it with the cytological method. It has thus been possible to assert the presence of a tumour at a stage when a slight microscopic haematuria would have left us in doubt and the patient in delay.

Field Experiment

Field investigation is properly the domain of the industrial doctor, and it is the most difficult.

In the last analysis it is upon field investigation that a final judgment must rest as to the relation between industrial environment and state of health. The difficulty does not lie in the recognition of this proposition, but in obtaining the opportunity and in devising the appropriate methods to establish such relations. To attain results which are soundly based and generally acceptable is a task requiring the cooperation of many disciplines. In the main, therefore, it is in the big organization with great resources that such studies can be made, but it is a parallel fact that in such organizations the environmental conditions are likely to be the best.

The practical application of the principles which emerge from field studies requires assiduity on the part of the industrial doctor and of those responsible for industrial hygiene, for this requires not only the willingness of employers to make money available, but also the willingness of workers to create it.

In conclusion, my object has been to indicate some of the things which concern those who are engaged in research in industrial health in the chemical industry, and some of the difficulties and dilemmas which arise. This kind of work is merely the preliminary to the application of the knowledge thereby obtained in the field and the factory. It is there that the ultimate goal set by James Mackenzie must be reached—the prevention of occupational illness.

I am extremely indebted to Mr. Kenneth Cooper and Mr. Leslie Hewitt for their kind cooperation in the preparation of the photomicrographs, and to my colleague Dr. J. G. S. Crabbe for Figs. 16 and 17. My thanks are due to Mr. Berezy, Mr. Crozier, and Mr. Denks for much technical assistance.

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