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IN 1931 Alice Hamilton published a review of the literature on industrial benzene poisoning up to December 1930, and laid special emphasis on the deviations from the classical picture of this form of intoxication which were revealed in a number of the published cases. She concluded: "If it is true that wide variations are found in the pathology of diseases of the blood, which have been the subject of extensive study, it seems that one is justified in believing that further study of chronic benzene poisoning will reveal a less one-sided picture than is at present accepted. The simple unvarying picture of this form of poisoning as it is found in the textbooks is certainly based on insufficient human material."

It has seemed to us worthwhile to carry on this study of the atypical forms of benzene intoxication, covering the publications of the 10 years which have elapsed since Alice Hamilton's review.

The classical picture of chronic benzene intoxication as seen in industry has been drawn by Santesson, Selling, and a host of observers and experimenters. Briefly stated it consists in a loss of red blood corpuscles, resulting in profound anemia; a loss of the elements and substances in the blood which are concerned in blood clotting, resulting in hemorrhage; and a loss of white blood cells (especially the neutrophiles) and of the substances in the blood serum which are concerned in defending the body against bacterial infection. On the basis of this description a standard has been formed for the diagnosis of benzene poisoning in industry and practical rules for its prevention have been laid down. Thus the well known "Final Report of the Committee of the National Safety Council on Benzol," May 1926, formulates these rules: "Any worker who on examination shows any of the following

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symptoms should be promptly excluded from benzene exposure. . . .

(a) Hemorrhages. . . .

(b) Decrease of more than the following amount from the employee's normal blood picture (normal conditions will be obtained from previous examinations of the individual employee).

(1) White cells, decrease of 25%; but in no case should an employee with a white cell count of less than 5,000 be continued in benzene processes.

(2) Red cells, decrease of 25%.

(3) Hemoglobin below 70%.

(Note: Reduction in white cells is the most important condition to be noted.)"

These rules have been followed by many factories and physicians and they have proved to be very useful, as we know not only from publications but also from our own practical experience.

The object of this study is to determine how far such diagnostic signs may be regarded as valid and sufficient.

I. HEMATOLOGICAL CONSIDERATIONS

EMIL SCHWARZ

The picture given by A. Hamilton (1931) does not need any completion. Her prophecy as to the result of further studies in the field of hematology as a whole and especially of chronic benzene poisoning has been confirmed. Yet the belief that anemia from benzene is an aplastic anemia with a corresponding blood picture still dominates medical practice and deviation from this type is still regarded as outside the picture.

The division of cases of chronic benzene poisoning into typical and atypical classes is based on the preponderant majority of cases and not on the actual morbid process engendered by the poison. Neither is our task accomplished by ranging the different appearances in the usual groups of blood pathology. One must trace the phenomena back to the primary processes which must be connected with the uniform cause. This fundamental problem is not restricted to hematology. It touches pathology as a whole and even industrial hygiene. The insight we may gain from this analysis will not only revise our estimation of the usual benzene prophylaxis but perhaps raise a doubt in our assumption of the unity of the damaging agent. Increasing experience and new methods of investigation are continually modifying our views in the field of hematology and tending to simplify them. The tendency now is away from a strict classification of blood diseases on the basis of the particular blood element involved (Ehrlich's aplastic anemia, Schultz' agranulocytosis, Frank's aleucia and panmyelophthisis, the symptomatic leucopenias, the thrombopenic purpuras) toward a realization that regenerative activity sets to work in all these cases with greater or less success, and the resulting picture depends on the ratio of regenerative activity to the destructive effect of the injurious agent.

The aplastic anemia of chronic benzene poisoning has been established

again and again but the four signs of aplasia, reduction of erythrocytes and leucocytes, a subnormal absolute count of lymphocytes in more severe leucopenia, and the absence of juvenile elements in the blood are not represented at the same time and to the same degree. Variations, even in otherwise typical cases, were noted in the earliest studies of benzene poisoning. A relative neutrophilia, instead of lymphocytosis, the appearance of more or less immature leucocytes, or of a rare normoblast, a high color index, an increase of reticulocytes or a polychromatophilia, all point to regenerative activity. All these seeming exceptions compel to the conclusion: The blood in typical cases of benzene poisoning is by no means devoid of regenerative signs. Regenerative activity is not abolished but combats constantly with more or less apparent effect the destructive influence of the poison.

Deviations of a higher order are seen in erythropoiesis, a temporary polyglobulia, a marked macrocytosis or megalocytosis, more numerous normoblasts, the occurrence of megaloblasts. Sometimes the picture of benzene anemia approaches that of pernicious anemia, an extreme degree of blood formation in response to the incessant call for reproduction. In our opinion even the maintenance of a normal count of red cells in the presence of other signs of damage in the blood is better explained by a stimulated compensating regeneration than by an uninjured erythropoiesis. The aberrations in leucopoiesis run in identical tracks. A count of normal or higher level in benzene anemia, an increased frequency of less differentiated elements, a higher degree of immaturity, the combination and accentuation of which may give the blood picture of myeloid reaction, are consequences of an excess of regenerative activity. Exaggerated immaturity with or without a raised leucocyte count turns the blood picture into that of leucemic or aleucemic myelosis and myeloblastosis, and benzene anemia has afforded instances even of this reversion of aplasia into its opposite. The problem of the relation of increased functional regeneration to leucemic proliferation lies beyond the limits of this essay.

Our enlarged and deepened experience permits full application of the principles developed above for aplastic anemia in general to the special questions of benzene poisoning. All the varieties of hematologic appearance, all the fluctuations in its course are to be explained by the conflict between the destructive action of the poison and the compensating activities of the organism. There is no greater stimulus for regeneration than the products of decaying cells of the same kind. Continuous destruction therefore automatically raises proliferation and the increasing stimulus spreads beyond the normal level of cell division, i.e., the myelocytes and the normoblasts, to the more primary stages, the myeloblasts and erythroblasts till it reaches the mother-soil of all blood cells, the reticulum. Either the stocks of newformed cells are time and again destroyed, in which case the result will be a hypo- or aplastic bone marrow, or regeneration surpasses destruction and the result is a gradual transformation of aplastic into hyperplastic bone marrow. The heterotopic metaplastic blood formation, especially in the spleen clearly illustrates the intensity

and the spread of the stimulus. A more complicated question, outside the range of this study, is whether intensity and spread of the stimulus and accelerated cell division furnish a sufficient explanation for the findings in benzene poisoning, or if beyond that a checking of the capacity to maturation must be admitted. The outbreak of the disease a long time after cessation of exposure suggests a deeper and more lasting shift in the biological disposition of the cells. The transformation into acute myelosis and, much more, the occurrence of chronic myeloid or lymphatic leucemia in consequence of benzene exposure, support such a suggestion at least for some cases. Anyhow, this experience is an important contribution to any future theory of leucemia.

We must conclude therefore that even in typical cases the tendency of blood forming tissues to maintain or to restore the stock is at work and that the atypical forms are those in which this tendency is not quite frustrated or is abnormally exaggerated. From this statement arise two questions of great importance for practical benzene prophylaxis.

One concerns the value of the usual danger signals. A fully reliable sign must fulfill the logical demands of sufficiency and of invariability. It is sufficient, when its presence positively reveals a pathological state, otherwise a non-existing damage may be simulated. Its presence in every case of benzene poisoning is necessary, otherwise a number of cases could escape identification. The inconstancy of other symptoms have resulted in a concentration of attention on the blood changes. The high sensibility of thrombocyto-genesis and the early appearance of hemorrhage makes it probable that thrombopenia is the earliest precocious change, but technical difficulties of thrombocyte counting and the wide differences in the accepted normal limits (300,000–750,000) make this sign ill-adapted for general use.

In this regard the count of red and white cells has many advantages. The limits adopted as critical anemia (see above) and leucopenia lie so far below the normal standard that this sign suffices to reveal a morbid state. However, according to our concept of the processes in benzene anemia it is impossible to be sure that all the individuals with a normal count are really unaffected by their exposure to benzene. In spite of the compensating activity, a continued exposure might mean a real damage. In Hunter's table of the blood findings in 89 workmen exposed to benzene a quite remarkable number show a leucocyte count between 10,000 and 17,000 with no evident reasons for this striking increase, and it would be a serious mistake to allow further exposure in such cases. Leucopenia, therefore, is not a necessary sign of benzene poisoning. A relative lymphocytosis does not tell us more than the absolute leucocyte count, because in all leucopenias the granulocytes suffer more and earlier than the lymphocytes and their drop implies arithmetically a rise in the ratio of lymphocytes. A very rarely encountered relative neutrophilia belongs among the compensatory reactions.

Similar considerations apply to the red cells. It may happen that a strong effort at compensation veils the chronic destruction. The paradox of initial polyglobulia reveals an excess of regen-

eration under the continuous stimulus, followed by exhaustion of erythropoiesis.

It is clear that no absolute value is attributable to any of those signs and the hope that progressive study of benzene poisoning will furnish such a simple sign is negatived by our increasing insight into the varying and interlocking processes of this intoxication and the circumstances under which it occurs. A full hematological examination of all cases will certainly yield better results. But if it is impossible to ask such a routine procedure from the medical staff entrusted with the task, the method proposed by the National Safety Council Report mentioned above seems still the most practical, especially if by a periodic supervision (every fortnight or month) we are enabled to follow the blood changes in the workmen.

The second question concerns the reasons for the variability in appearance and in the outcome of the effects engendered by a seemingly uniform agent. Here the two factors of the injured subject and the active cause enter into consideration. Individual constitution and degree of sensitivity remain mere words so long as they are not determinable by observation. In any event, constitutional differences can never account for "epidemics" of benzene poisoning because there is no reason to assume a change in selection of the working force. Our attention, therefore, is directed to the variations in exposure and to the poisonous substance itself, a matter dealt with in the following paragraphs.

II. STATISTICAL AND INDUSTRIAL HYGIENIC CONSIDERATIONS

L. Teleky

We have attempted in the following table to collect all the serious cases of chronic benzene poisoning published after the report by A. Hamilton as far as they were accessible to us. Naturally we cannot claim completeness, but we believe that only a few cases have escaped us, such as cases from reports of factory inspectors in European countries, the details of which we could not obtain, and also some in reports of Industrial Commissions of several of the states in this country. A few of these reports which were at our disposal did not differentiate between damage caused by benzene and those caused by its derivatives. We have tried to avoid double counting of the same cases as far as possible.

A large number of publications in the last decade report the results of periodical examinations of benzene workers; single serious cases induced examinations of all other workers of a plant. Therefore we have now more reports about single or repeated examinations even of very slight cases than in previous years. We have included only serious cases in the table and we qualified as "serious cases" only those with *less than 3,250,000 erythrocytes*. In one case the number of erythrocytes in a single examination was 3,200,000, but the counts before and after were markedly higher, and therefore we considered the case not a "serious" one. That certainly is an arbitrary division; to be exact every case should be judged by its entire clinical picture, but if we did that the judgment would still be arbitrary and the limitation less clear. We call "typical" those cases which

show: *hemorrhage, decrease of red and white blood corpuscles and, if a full blood picture is given, absolute and relative neutropenia and thrombocytopenia.*

TABLE 1

TYPICAL AND ATYPICAL CASES OF SERIOUS BENZENE POISONING REPORTED, 1930–1939

COUNTRY	UP TO 1929 BUT REPORTED LATER	1930	1931	1932	1933	1934	1935	1936	1937	1938	1939	1930–39
England												
Typ...			1 (1)		1 (1)	3 (3)		1 (1)				6 (6)
Atyp..												0
France[a]												
Typ...		2 (1)			11 (9)[b]	3 (2)	1 (1)	4 (2)	3 (3)	18 (4)[e]	1	43 (22)
Atyp..			1 (1)					1		2		4 (1)
Germany												
Typ...	1 (1)		1 (1)	2	7 (2)	7 (2)	1 (1)	8 (2)		2 (1)		28 (9)
Atyp..	2 (2)											[f]
Austria[a]												
Typ...			12 (5)					8				20 (5)
Atyp..			4									4
Russia												
Typ...	1		1									1
Atyp..												0
Italy												
Typ...						1	2 (1)	9 (3)				12 (4)
Atyp..												0
Belgium												
Typ...							5					5
Atyp..							1					1
Rumania												
Typ...							1					1
Atyp..												0
Nether-lands												
Typ...									2 (1)			2 (1)
Atyp..												0
U. S.												
Typ...	2 (1)	1 (1)	1		1 (1)	4 (3)[e]	1 (1)[e]	1	3 (3)[d]	9 (4)	2 (1)	23 (14)
Atyp..	1 (1)	1 (1)						2 (2)		1	2 (2)	6 (5)
Total												
Typ...	4 (2)	3 (2)	16 (7)	2	20 (13)	18 (10)	11 (4)	31 (8)	8 (7)	29 (9)	3 (1)	141 (61)
Atyp..	3 (3)	1 (1)	5 (1)				1	1 (2)		3	2 (2)	15 (6)

Numbers of fatalities are given in parentheses.

[a] Regarding cases of Dimmel (Austria) and Sabrazès (France). See text.

[b] Of 8 fatal cases, no clinical picture is presented (Heim de Balsac and Agasse Lafont).

[c] No full description given.

[d] In one case no full description given.

[e] Mignolet's 15 cases probably typical.

[f] A remarkable case of Kern's is omitted as it is not serious in our sense.

The cases of Dimmel were especially difficult to classify. He published the histories of 66 cases observed among workers of a factory which was closed down after the first fatal cases. Examination of some of these workers was made some time after the factory was closed. Selecting from his table the cases which come under our classification, we find 12 typical and 4 atypical cases. But Dimmel himself calls 15 cases serious in addition to 5 fatal cases, and his judgment is probably better than our classification for statistical purposes. Among these 20 cases we could call 17 typical, 3 atypical.

We include in the table all cases caused by benzene or by benzene mixed with other substances, if the benzene seemed to be the chief agent. In many cases the composition of the solvent was not clear. (We discuss later cases in which other compounds were employed.) But in all probability benzene was inhaled too. In our compilation of cases, we did not include those of Sabrazès and his collaborators: three cases of leucemia. One man worked with lubricating oil; the other worked on the second floor of a factory on the first floor of which benzene derivatives were employed. The only open connection between the floors was a staircase. The first man was a garage proprietor and mechanic. There is not the slightest possibility that these men were injured by benzene.

We have arranged the cases according to the year of death or of termination of observation, because often the onset of the illness is not made clear. Dates given are not those in which the material was published. Unfortunately in some cases the date of illness is not given and must be approximated. Furthermore, some authors (Heim de Balsac and Agasse Lafont) tell us nothing specific about the clinical picture, but if Mignolet's description is accepted, the cases may be considered typical, in our sense. But these deficiencies do not alter the general picture gained from the table.

Of more importance is the fact that perhaps a number of cases of poisoning have not been reported and that even more have gone unrecognized. One may assume this from the history of series of poisonings in certain factories. Such a series explains also the frequency in one year (Dimmel, 1931; Heim de Balsac and Agasse Lafont, 1933; Mignolet, 1938).

The number of cases is very high in France (47) and may be explained by the nature and organization of its industry. In this country the number (29) is relatively low, but is increasing. The totals, however are very high: in 10 years there have been 156 serious cases with 67 deaths, and one may expect that additional cases for 1939 will be published later. Concerning the proportion between typical and atypical cases we have 141 typical and 15 atypical cases between 1930–1939. That means 9.6% of atypical cases. If we consider different single countries, the numbers are mostly too small for statistical consideration, but it may be mentioned that the proportion between atypical and typical cases in France is 4:20, but in the United States 6:23. The number in single years is too small for statistical purposes but we may note an apparent increase in the proportion of atypical cases compared with the typical, especially in the American list. In the last 5 years we find 5 atypical and 16 typi-

cal, in the first 5 years only 1 atypical against 7 typical. It is not possible to draw definite conclusions from such small numbers, especially in view of the possibility of different opinions concerning what constitutes an atypical case. But it is, after all, probable that the atypical cases have increased in recent years and chiefly in the highly developed American industry.

To what factors may this increase be attributed? Certainly not to advanced knowledge of hematology nor finer methods of examination. Changes in the constitution of workers or in their nutrition (vitamin C content) could change the clinical picture, but we have no reason to assume such changes in recent years. A different rate of absorption of the poison might possibly alter the clinical picture. Lignac and Emile-Weil believed that the cases of benzene leucemia they discovered were to be explained on the ground of very slow absorption of the poison, the men having worked many years before the blood disease developed. But the job of one man was considered by his fellow workmen to be very dangerous. At present we have no proof of the different effect of very small doses as compared with larger.

There may be a change in the injurious material, as a consequence of mixing other solvents with benzene, especially its homologs.

Changes in the Use of Benzene and Its Homologs

The great confusion caused by the similarity of the words "benzene" and "benzine" has almost disappeared from the literature of today, but occasionally it is still found, even in scientific work.

Besides the pure crystallizable benzene (C_6H_6) used only in certain chemical productions, the following different sorts of benzene are used commercially.

	BENZENE (C_6H_6)	TOLUENE ($C_6H_5CH_3$)	XYLENE ($C_6H_4(CH_3)_2$
Benzene 90...	84%	13%	3%
Benzene 50...	43	46	11
Benzene 0....	15	75	10

In some countries (e.g. Germany) solvent naphtha is called "solvent benzene" and there is also a "heavy benzene," neither of which contains any benzene, only xylene and cumene.

These proportions vary in practice and there may be impurities present, such as thiophene, paraffins, carbon disulfide.

It is evident from these statements that when the commercial nomenclature "benzene" is used it may signify a hydrocarbon containing only 15% benzene or even no benzene at all. The use of the word benzene and its homologs is still less accurate in workshops: Stocké, for instance, tells us, that a liquid which in the factory was called "xylene" was pure toluene. Brindeau reports that his patients inhaled vapors of "impure xylene," but the liquid was shown to contain 30% benzene and a considerable amount of carbon disulfide. It is often very difficult for the industrialist to know what he is using and this adds to uncertainty in some publications.

The composition of cements, thinners, coatings and inks has changed decidedly in recent years. Rubber cement, which gave rise to the first published cases of industrial benzene poisoning (Santesson's) was then prepared in the factory and only benzene was used. L. Greenburg described this

procedure in 1926 and I saw it 10 years ago in some of the largest rubber factories in Germany. Later on rubber cement came into increasing use, especially in shoe manufacture, where it replaced nailing and sewing, but this cement is now produced in factories and sold to the users. Many different compositions of rubber cement are described in trade journals and the solvents used are benzene, gasoline (benzine) petroleum spirit, solvent naphtha and "non-inflammable" solvents. So it is easy to see that the word "cement" does not disclose anything about the constituents.

As to the extent of the use of benzene in American industry at present, it is hard to get detailed information. The Report of the Committee of the National Safety Council on Spray Coating, 1927, states that the use of benzene in lacquers has been discontinued by practically every manufacturer because of its recognized danger to health. However, in the same report we find that H. F. Smyth reports that benzene vapors in the air of 5 plants contained an average of 375–1880 p.p.m. and that among 14 lacquers 9 contained benzene. Among Hunter's cases, described in 1939, there were some who had worked with lacquers. All this shows that benzene is still used in lacquers in this country. But there are reports from this and other countries showing that toluene, xylene and other solvents are being used in varnishes to an increasing extent.

A new source of benzene poisoning is *rotogravure printing* ("heliogravure" in France, "Tiefdruckverfahren" in Germany, "stampa a rotocalco" in Italy). It seems that at first harmless inks were used, but very soon benzene became the solvent agent and was only gradually replaced by less poisonous solvents when ink manufacturers found less poisonous inks just as satisfactory. Greenburg and his collaborators tell us that in one plant for colored inks the solvents used contained 70–75% benzene by volume, for black inks from 30–35%, for the thinners 60–80% benzene. In all plants "the benzene content of the thinners varied from 20–80% by volume. In addition, other volatile solvents were present, such as toluene, xylene, methyl-ethyl ketone, petroleum naphtha, ethyl, butyl and amyl acetate and butyl and amyl alcohol."

Nothing is said in many publications about the quantity of these other solvents in the mixtures nor about the vapors of these solvents in the air. The vapors of benzene were measured, but that these other vapors may also be important will be shown later. Mixtures used in German rotogravure printing, as given by Bachmann, may be quoted here:

Plant 1: 41% Xylene, 59% Benzine, 3% Benzene
Plant 2: 50% Xylene, 50% Toluene
Plant 3: 60% Xylene, 40% Benzine
Plant 4: 15% Xylene, 80% Benzine, 5% Ester mixtures

In summarizing we want to repeat: In contradistinction to former times we can no longer depend on the name of the job (as cementing, spreading, color mixing, rotogravure printing) to tell us whether the workers have been exposed to vapors of benzene alone or in mixtures. We must take into consideration also other solvents, especially toluene and xylene. The composition of the vapors necessarily differs from the composition of the solvents, especially if there is a mixture

of benzene and its homologs. The boiling point of pure benzene is 80°C., of commercial toluene 109–111°C., of xylene 138–142.3°C., of commercial xylene, 135–145°C. The vapor pressure at 40°C. is for benzene 181.1, for toluene 59.1, for xylene 19.48–23.7. Therefore, the content of benzene vapors in the air is larger than its proportion in the mixture.

The Effects of Toluene and Xylene

Animal experiments on the effects of the higher homologs of benzene, toluene and xylene have been carried out for many years. The earlier experiments are reviewed by Batchelor in his part of the "Final Report on Benzol." Batchelor himself tested them on animals and found that toluene and xylene have a more powerful narcotic effect than benzene. At autopsy the majority of the animals which inhaled toluene "presented microscopically a definite hyperplasia of the bone marrow, of the Malpighian corpuscles of the spleen and of the germinal centers of the lymph nodes." In xylene poisoning he found that "microscopically slight hyperplasia of the bone marrow was present."

Selma Meyer in 1928, upon my suggestion, examined the blood of a number of men who had worked for the month preceding with a mixture of xylene, toluene and benzene in the proportions of 5:4:1. The single positive finding was a slight lymphocytosis (35–40%) with an increase in large lymphocytes. Ferguson, Harvey and Hamilton reported (1933) the first fatal case, caused by a solvent containing toluene (about 45%), but no benzene. The man began work in 1919, fell ill in March, 1932 and showed hemorrhagic spots on his tongue, later bleeding from the gums and subcutaneous hemorrhages:

	Blood findings			
	Red cells	Hb	White blood cells	Polymorphonuclear
	millions			
Aug. 15	4.00	75	2200	
Oct. 4	2.60	82	1900	23.9% (449). Polychromasia
Nov. 11	3.30	72	2400	5.3% (127). Red cells irregular, some macrocytes. Polychromasia
Dec. 23	2.21	50	1200	5.5% (67). Polychromasia. 10 nucleated red cells. Platelets numerous

The man developed gastroenteritis and pneumonia and died December 24. The autopsy showed the bone marrow of the femur shaft in a state of aplasia, although it was really a red marrow. The lymph nodes demonstrated a pronounced proliferation of the reticular cells, absence of germinal centers and an apparent fibrosis.

The authors, reviewing the literature and the history of this and their own animal experiments, conclude that benzene is a more powerful poison because it is more volatile than toluene and can therefore reach higher concentrations in the air, but because of this greater volatility benzene "is eliminated more quickly and its effects are less lasting than those produced by toluene."

G. de Oliveira reports a fatal case attributed to xylene. A man who had inhaled xylene vapors for a long time died and the autopsy showed changes

of an aplastic anemia, serious damage to the bone marrow and also atrophy of the lymphoid tissue of the spleen and lymph nodes.

The following two fatal cases, published by S. Hirsch, should be mentioned also: These two men worked in a rotogravure printing shop. Analyses of the inks made several months later showed that the "ink" contained about 16% xylene, a thinner with 29% of a mixture of benzene and toluene and 64% xylene; another substance used alternatively had 3% benzene and toluene and nearly 87% xylene." Both men died of aplastic anemia, sepsis and endocarditis. The femur of one man showed a red bone marrow, of the other, a fatty marrow. Examination of the co-workers (performed a long time later) showed in nearly half less than 5 million erythrocytes, but no changes in the number or character of the leucocytes. The author thinks that xylene was the cause of death. I am not sure of it, because analyses of the material and examination of the other workers was performed a long time after the two fatal cases occurred and such accidents are usually followed by a prompt change in the material used.

Even if we add these two cases *the number of deaths caused by xylene or toluene is very small in proportion to the* widespread use of these substances in recent years. But that disturbances of health less serious in character may be caused by these solvents is made clear by a large number of studies of workers in plants which use mixtures containing benzene in small percentages and its homologs, or these homologs only, such as plants for rotogravure printing and for every kind of varnishing, spray coating etc. Most of these publications are by German authors. Those which refer to plants using homologs only are the most important.

Adler-Herzmark and A. Selinger published reports on workers using benzene or its homologs. I will discuss only the latter. Among those using toluene a moderate degree of anemia was found, no count being below 3½ million; also anisocytosis and poikilocytosis; and a relative lymphocytosis with an absolute leucopenia of low grade. In another investigation users of xylene or toluene showed an absolute neutropenia and alterations in the erythrocytes. In 11 women using a solvent with 15% to 17% toluene, three showed granulocytopenia (1850 to 2800) with lymphocytosis.

Stocké was the first to report injury to workers in rotogravure printing (1929). In these shops pure toluene was used. The workers complained of irritation of the conjunctivae, headache, vertigo, sleeplessness, anorexia, palpitation and stomach troubles. Among 10 who complained of illness, seven had a relative lymphocytosis between 30% and 46%, in a count of 7300 to 8800 leucocytes.

A. Brandt examined two rotogravure printing shops, one using as solvent no benzene but 25% toluene, 70% xylene and 5% cumene; the other a mixture of 75% toluene, 10% xylene and 15% benzene. In both shops there were many complaints of headache and stomach trouble and in both the blood pictures showed changes in the erythrocytes and a leucopenia (down to 2800) with marked neutropenia (down to 45%). The blood changes were more pronounced in the first shop than in the second where

benzene was used but where the ventilation was better. Litzner and Edlach report the results of an investigation of 7 workers who used "pure toluene." Here again the number of erythrocytes was slightly diminished but there was no anisocytosis or poikilocytosis. In three the neutrophiles were less than 55% of the white count.

H. Gerbis examined the workers of 7 rotogravure printing shops. He gives us exact statements about the material used in five of them and from the results of the examinations (which are not always very clear) we quote as follows:

	Number of workers	Leucocytes 6000 and below	Lymphocytes	
			Over 35%	Over 50%
A plant using benzene mostly	166	77 (46.8%)	72 (43.3%)	2 (1.25%)
Two plants using xylene, toluene and 10% benzene in the solvent	81	12 (14.82%)	55 68%	8 9.9%
Two plants using preponderantly pure xylene	67	5 (7.8%)	40 (60%)	11 (16.5%)

Therefore we may conclude that benzene damages chiefly white blood cells as a whole, but its homologs, especially xylene, damage the granulocytes more than benzene does.

Brachmann reports on an examination of 4 rotogravure printing shops using the material given above. In the first, using 3% benzene in the ink, no injury to the leucocytes was found, but two workers complained of nose bleed. Brachmann believes that the effect of chronic xylene and toluene action is a real damage to the neutrophilic granulocytes. But he also often found anisocytosis and poikilocytosis. There were complaints of nervousness, headaches, insomnia, irritability and vertigo.

Lind (1938) examined 230 spray coating workers, who were exposed principally to xylene and toluene, but also to other solvents, such as acetates, alcohols and esters. In some cases benzene too seemed to be present in small amounts. He writes: "The symptoms which characterize the health picture of spray coaters are nervous ones." Leucopenia was present in a few workers (20); in 33 there was an absolute neutropenia. More often there was an absolute lymphocytosis (61 over 3000, 103 from 2500 to 3000). As no distinction is made between the men working with different materials this publication is not very useful for our purpose, which is to make evident the effect of xylene and toluene as far as it is possible. There are other publications about rotogravure printing, but they are of no help to us because the injurious substances are not exactly described. For instance, Nelken writes about the intoxicating effects of "xylene (respectively toluene and benzene)." Kahle's subjects were exposed to the "effect of benzene and its homologs xylene and toluene," and later, he says, to the effect of "xylene and toluene." The nervous symptoms: headache, vertigo, insomnia, chronic fatigue, are in the foreground, besides vasomotor lability. In the cases of Castrovilli, the rotogravure printers worked with "xilolo," actually a mixture of benzene, toluene and xylene.

We have to conclude that from the standpoint of industrial hygiene, xylene and toluene (the published material is not extensive enough nor de-

tailed enough to allow us to treat these two substances separately) are far less dangerous than benzene. In spite of their abundant use, the number of fatal cases is very small (two positive cases, one caused by xylene, one by toluene, and two other probable cases in the literature). In the other reported cases the alterations of the blood picture are far less serious than those caused by benzene. We cannot decide, however, whether the less damaging effect is owing to the lessened evaporation or to the lesser toxicity of the same amount of vapor. There is no doubt that certain differences exist between these two substances and benzene in their qualitative effects on the blood picture. They often produce alterations of erythrocytes (poikilocytosis, anisocytosis), they do not influence all the leucocytes to the same extent as does benzene, but they have a greater injurious effect on neutrophiles. Therefore, we ask ourselves whether or not deviations from the typical blood picture in cases of supposed benzene poisoning (at least slighter deviations) should be traced back to the combined action of these substances. But we must also remember that the effect of two toxic substances may not necessarily be the sum of their effects, but may give an entirely new clinical picture.

One clinical effect is much more characteristic of these two homologs than of benzene itself: the effect on the nervous system. In rotogravure printing and spray coating the following complaints stand in the foreground: headache, confusion, vertigo, fatigue, insomnia and stomach trouble. This action on the nervous system is confirmed by animal experiments showing that the anesthetic effect of the toluene and xylene is greater than that of benzene. These symptoms are the result more of a slight acute poisoning, newly acquired every working day, while the blood changes are the consequence of chronic poisoning.

At all events, the effect of toluene and xylene, although rarely causing death, must be taken seriously into consideration from the clinical and the hygienic standpoint, even if benzene too is present in the liquid or solvent used. The "Final Report" quoted above, decided that the "allowable limit" of benzene in the air should be set at 100 p.p.m. Later observers (Bowditch and Elkins) urge a lower figure, 75 p.p.m., and Hunter declares "that the only really safe concentration of benzene is zero." The reason for this change of opinion may be that earlier examinations, made with less exact methods, caught benzene and its homologs together, the amount of the latter being small at that time. But today the vapors of benzene alone are captured and the vapors of the homologs, although today they form a greater part of the contamination of the air, are neglected.

Other Admixtures in Solvents

In their effect on the blood producing organs there are some other substances to be considered in modern solvents of rubber, in cements, in inks, coatings and thinners. There are reports about blood changes caused by benzine, but some of them concerning human beings seem to be not very reliable. Schustrow and Salistowskaja in describing their animal experiments refer also to a publication by myself and another by Brücken as examples of

blood changes in man caused by benzine, but both of us wrote under the title "benzene poisoning" about workers of the same factory. Duvoir, Pollet and Arnoldson present a case of polyneuritis, especially of the lower extremities showing also serious blood changes: 1.5 million erythrocytes, 9500 white blood cells with 81% neutrophiles. The autopsy showed fatty marrow. This woman had worked many years with benzine. I discussed this remarkable case in a French journal (La Medicine du Travail, 1938). Adler-Herzmark reports on two workers, who, in the production of adhesive plaster, used 35 l. of benzine daily, containing 3.3 vol. % of aromatic compounds. They had pharyngitis, acceleration of the pulse and tremor. One of them had 6.2 million erythrocytes with anisocytosis and poikilocytosis, 11,700 leucocytes with 52.4% neutrophiles. The other worker showed 4.2 million erythrocytes with anisocytosis, 74% hemoglobin, 5390 leucocytes.

Engelhardt discusses some Russian publications, reporting blood changes in benzine workers. The most remarkable effects in Russian workers in rubber and other factories will probably never be cleared up entirely, but the cause seems to be the composition of Russian benzine (different from American) which contains cyclic-hydrocarbons, and carbon bisulfide in varying amounts.

Gran describes the case of a man who as a consequence of chronic benzine poisoning had 1.58 million erythrocytes, 28% hemoglobin, poikilocytosis, anisocytosis, 11,840 leucocytes with 81% neutrophiles, 11% lymphocytes, 6% eosinophiles. The man recovered. I myself have observed among people working with large amounts of evaporating benzine, attacks of fainting. One case suffered from serious polyneuritis, but not one showed any blood changes. Still there remain, as we saw above, 4 cases of blood changes attributed to benzine, at least two of them reported by a very critical observer. This is a very small number when one considers the widespread use of benzine. It would seem that there must have been some exceptional circumstances in these cases, perhaps the unsuspected presence of other harmful substances.

Solvents often contain other compounds, such as butyl alcohol, which, according to H. F. Smyth, produces a decrease of red cells with a relative and absolute lymphocytosis; methyl alcohol, "a true hematoxic" according to Tyson and Schoenberg; butyl acetate, etc. The use of mixtures has increased in recent years, replacing the use of benzene alone. The effect on the blood when two or more substances act simultaneously may be to produce a different clinical picture and such a possibility should always be considered when a given case presents deviations from the "typical picture" of benzene poisoning. The coincidence of an increasing use of mixed solvents in American industry and of increasingly frequent occurrence of atypical cases of benzene poisoning in American literature point to this conclusion. Only clinical studies combined with exact chemical examination of every substance used and every vapor contaminating the air (not benzene only) will suffice to clear up this problem.

Industrial Hygiene

It is clear that the harmful effects of toluene and xylene are far less

serious than the effects of benzene, and therefore it is desirable to replace benzene by its homologs, or better, by still less harmful substances.

Lind tells us that in Danish factories the use of benzene in varnishes and lacquers was greatly decreased in response to the wishes of the public. German factories producing inks for rotogravure printing have taken pains to exclude benzene, and Gerbis tells us that in these plants benzine is used to a great extent now. The German government had made experiments (Koldenhofe) in substituting benzene in cements for waterproof material; for usual purposes replacement by benzine is possible, but for some specific purposes a small amount of benzene is still needed.

Royal decrees in Belgium from 1936 to 1938 forbade the use of benzene containing cements in the manufacture or repair of waterproof clothing, and the use of varnishes in mirror manufacture, of inks, thinners or detergents in rotogravure, which contain more than 1% of aromatic compounds.

Evidently the substitution of benzene by other solvents is possible. To make it possible for the customer to buy innocuous material if he wishes to do so, to enable inspectors to carry out the regulations of the government, the material brought on the market containing dangerous substances must be recognizable as such by proper labeling. That is an old demand of industrial hygienists. Belgium has such a law (January 23, 1937), Germany is introducing it. The Massachusetts Benzene Labeling law (Chapter 149, General Laws, Acts of 1933 and 1935) prescribes exactly how every receptacle with material containing benzene must be marked.

However these ideas may be executed in a country or state, restriction of the use of benzene is necessary; but as long as its use is continued, medical supervision is essential, with complete blood examination every month at least. This recommendation was made in the often quoted National Safety Council report. When toluene or xylene are used, it would be sufficient to make such an examination every 4 months, or even every 6 months. In some States the Labor Department has the right to order such periodical medical examinations, for instance in New York, according to the Labor Law §28,2. The French government prescribed a periodic medical examination of workers exposed continually to benzene vapor (decree of Oct. 29, 1939).

Summary

Analysis of blood formation in benzene poisoning shows that the balance of destructive and regenerating processes determines the resulting blood picture and the state of the blood forming organs. A review of all the cases of poisoning that have been published in the last 10 years shows a large number of serious cases. There are 156 cases with 67 fatalities, besides a large number of slight intoxications. The number of cases in this country is increasing markedly. Toluene and xylene are more widely used today than in earlier years, often mixed with benzene, while formerly the latter was used alone. These homologs have, as industrial poisons, a greater effect on the nervous system than benzene but they may also injure the blood-forming tissues and cause death, although very rarely. Changes in the blood differ

to some degree from those caused by benzene. There are also other substances present in mixed solvents, such as benzine, butyl alcohol and acetate, methyl alcohol, some of which may have an influence on the blood-forming organs, at least under certain circumstances.

As the combined effect of several harmful substances is not always the same as the sum of the individual effects but may result in an entirely new clinical picture, an atypical case of benzene poisoning should be viewed as possibly caused by a mixture of different toxic solvents. This is indicated by the fact that atypical cases seem more frequent in recent years, and especially in this country where the use of mixed solvents has greatly increased.

To clarify the effect of these mixtures on blood formation, we need exact determinations of all the air-contaminating substances, not only benzene. The restriction of the use of benzene, its replacement by less dangerous (preferably quite innocuous) solvents, is imperative in any work where evaporation into the air breathed by the workers occurs.

As long as benzene is used, medical supervision is indispensable and accurate blood examinations must be made each month at least, while where toluene and xylene are used, an examination every 4 to 6 months is sufficient.

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BOOK REVIEWS

STUDIO SULL' ASBESTOSI NELLE MANIFATTURE DI AMIANTO. (STUDY OF ASBESTOSIS IN THE MANUFACTURE OF ASBESTOS.) *By Enrico C. Vigliani.* Paper. Pp. 74. Ente nas. di Propaganda per la Prev. deg. Infortuni, Turin, 1940 (40 l.)

The author surveys briefly the literature and gives a good description of processes in asbestos textile work, especially in 4 factories. After some chemical examination of different kinds of asbestos, the results of dust counts made by thermal precipitator and konimeter are quoted. 40% of the particles are under 1 μ; dust counts ranged from 110–5300 per cc., being highest in the early stages of the work; in the carding room the count was 360–3300, in the spinning room 80–420, and in the weaving room, 100–2600.

In three plants each worker was examined and in the fourth, only those who had worked more than 6 yrs.; altogether 439 persons were included. 350 were x-rayed, 200 of them twice. Most of the workers were women. Among the 150 persons working more than 6 yrs., 60% had coughs, 35% were dyspneic, 27% had slight dulness at the bases of the lungs, and 39% had crepitant rales. The corresponding figures for the 72 persons suffering asbestosis were 82%, 65%, 51% and 70%. Of all the workers, 9.6% had asbestosis warts, 66% of those who worked more than 6 yrs. had fibrosis, and in the preparation process, 10 of 11. The frequency of asbestosis increases with the average concentration of inhaled dust. It is remarkable that there was no case of tuberculosis among the workers and no case of pulmonary cancer, although there was one case of malignant lympho-granuloma of the mediastinum.

This carefully prepared publication is accompanied by a large number of valuable illustrations, first of the manufacturing processes, then of the dust, and finally of the roentgenograms of 49 cases of asbestosis in different stages.—*L. Teleky.*

PUBLIC HEALTH ADMINISTRATION IN THE UNITED STATES. *By Wilson G. Smillie.* 2d edition. Cloth. Pp. xiv + 553. Macmillan Co., New York, 1940 ($3.75).

This is a second edition of a book originally reviewed 4 years ago in this Journal (Vol. 18, p. 89). The original edition has been enlarged by about 100 pages, brought up to date and materially strengthened. It gives a thoughtful and well balanced view of the field and should be valuable to the industrial hygienist who desires to understand the general public health background of the community in which he works.—*C.-E. A. Winslow.*

STATISTICAL CALCULATION FOR BEGINNERS. *By E. G. Chambers.* Cloth. Pp. viii + 110. Cambridge University Press, London, 1940. (7 s. 6 d.)

The non-mathematical student or research worker often experiences difficulty with the calculations involved in even the commoner statistical methods, and he will welcome the appearance of this little book. It is not in any way intended as a textbook on the theory of statistics, and only contains enough theory to enable the reader to understand and apply the methods described. Its one purpose is to explain as simply as possible how the calculations should be performed. Mathematical ability on the part of the reader is not assumed; all the calculations described involve the use of arithmetic only. A worked example of each method given is provided, and exercises with answers are a useful feature.

The author has addressed the book chiefly to students of psychology and the other biological sciences, but it should be of great use to any who have to employ elementary statistical methods and many research workers will find it a useful desk book.—*T. Bedford.*

A CHEMICAL AND PHYSIOLOGICAL INVESTIGATION OF ELECTRIC ARC WELDING*

III. Coated Welding Rods

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PREVIOUS papers (1, 2) in this series have cited literature sources and the general purpose of these investigations. Electric arc welding with bare washed rods was dealt with in one article (1) showing the influences which are common to all electric arc welding with metallic electrodes, while medical situations have been emphasized in the second publication (2).

The present paper is devoted to results from similar experimental investigations in which a widely used coated electrode has been studied. Here the general factors encountered in the simpler case of bare rods are modified, and in addition the probability of harmful actions from new chemical agents in rod coatings arise. For this reason a rod containing only a few toxic chemicals in the coating was desired. The rod coating chosen was more complex in chemical nature than we preferred but practical industrial considerations dictated its selection.

The investigative approach to the problems of a coated rod was identical to that for bare rods in that the effects of various gases and fumes on animals over a period of weeks were determined under controlled conditions; during the entire time these substances were quantitatively measured. In addition some new features of work were provided including blood counts, methemoglobin determination, x-ray examination and intraperitoneal injection.

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Chemical and Physical Data

The same equipment and methods of sampling employed in the investigation on bare rods were used in the present study. The methods of analysis were the same when identical substances were estimated (1).

Comparisons between the amount of "nitrous gases," ozone, CO, Cl_2 and iron and manganese fumes found with bare rods are therefore on an equivalent basis in the two investigations. Approximations were made of the amounts of silica and TiO_2—the major new components found in the coated rods. All exposures in this experiment were produced by 44 v. and 300–350 amp. across the arc.

A. Analyses of Electrode, Coating and Fumes

The analyses of the rod coating in this investigation is shown in table 1.

The analysis of the coating was checked by several observers using

various standard colorimetric and gravimetric methods. The only disagreement was in the amount of phosphorus which was found only in traces. Taking this into consideration, the total constituents established would be reduced by 0.4% to 98.6%, in place of the 99.0% reported.

However, on the basis of the analytical data for airborne dust and fume in the exposure chamber as shown in table 1, such minor discrepancies as reported in the coating analyses are probably negligible. The components which appeared in the coating are diminished in the fume, presumably because of their inclusion in the slag, and the added iron from the core.

The rod itself was found to contain 99.5% Fe, 0.4% Mn and negligible amounts of other substances as P and S (less than 0.05% each). This is approximately the same composition as the bare washed rod previously reported on so that changes in the gaseous and fumous concentrations can be attributed to the effects of the coating on the arc and the added factors resulting from chemicals in the coating itself.

TABLE 1

ANALYSIS OF ROD COATING AND AIR-BORNE FUME

	ROD COATING	AIR-BORNE FUME
	%	%
Moisture, organic volatile matter	6.9	1.70
SiO_2	20.5	8.40
TiO_2	41.5	5.40
MnO_2	10.9	5.00
CaO	2.5	
CO_2	1.4	
MgO	5.4*	
$Mg_3(PO_4)_2$ (P_2O_5—0.65%)	1.1	
Fe_2O_3	8.8	79.00
Total	99.0	99.5

*Net MgO = 5.9%—used 0.5% MgO with 0.65% P_2O_5.

B. Gases

The quantities of gases evolved by the welding process using coated rods varied greatly from the amounts found when welding with bare rods. The percentages of oxygen were normal (table 2) with no value less than 20% O_2; no excessive CO_2 was found. No CO was detected though small amounts of organic matter were present in the coating.

TABLE 2

OXYGEN AND CARBON MONOXIDE CONCENTRATIONS

SAMPLING TIME	OXYGEN	CO_2
	%	%
16 min. 8:58	20.6	0.22
Immediately 9:13	20.7	0.21
16 min. 12:58	21.0	0.20
Immediately 1:13	20.9	0.00

TABLE 3

OZONE CONCENTRATIONS, IN P.P.M., S.T.P.

1 IN. FROM ARC	4 IN. FROM ARC	CENTER OF CHAMBER
2.07	0.72	0.36
1.10	0.28	0.16

The ozone concentrations (table 3) were less than those found when welding with bare rods at 44 v. and 300–350 amp. This diminution was most marked close to the arc; while the concentrations near the animals were less than previously noted, they were

of about the same order. It was assumed that the coating on the rod resulted in a shield which protects the O_3 from the ultraviolet light, or that the O_3 is kept from contact with the available energy across the arc. The decreased amounts present as the distance from the arc increased are similar to the decreases noted in the experiments with bare rods except for the variations in quantity. No chlorine or chlorides were found at any time in the exposure chamber.

TABLE 4

ANIMAL EXPOSURES

		NO_2	Fe_2O_3	Mn	EXPOSURE TIME	
		p.p.m.	mg/cu.m.	mg/cu.m.	hr.	min.
High	1*	21	446.0	16.5	12	16
	2†	31	605.3	21.2	61	20
Low	1*	13	176.0	5.0	12	16
	2†	21	292.3	10.1	61	20
Intermediate	1*	12	270.0	9.5	21	28
	2†	22	439.4	15.25	107	20
Average	1*	14	290.5	10.1	46‡	
	2†	24	444.1	15.45	230‡	

* 8:30 a.m. to 9:30 a.m.
† 9:30 a.m. to 2:30 p.m.
‡ Total.

"Nitrous Gases." Samples for "nitrous gases" were all taken at the armports as conditions at that point were previously shown (1) to be representative. Table 4 provides a summary of conditions which existed during this experiment showing average concentrations of 24 p.p.m. of "nitrous gases" always computed as NO_2 for the 5 hour period and less than 20 p.p.m. of NO_2 for the first hour of exposure. Comparing this with the average concentrations from bare rod experiments using 44 v. and 300–350 amp. and all conditions the same, shows that this is about one-third the average concentration of 72 p.p.m. for the 5 hour period and the low for the 8:30 to 9:30 period is also about one-third of the "nitrous gases" produced.

Similarly we have made comparisons between the ratios of nitrites and nitrates in the cases of bare and coated rods (table 5). The ratios show about 4 times the quantity of "nitrous gases" when tested for all nitrates.

Three methods were used for the determination of nitrites. The sulfanilic acid method was used in previous experiments but neither the brucine method (3) nor the modified phenoldisulfonic method. The phenoldisulfonic acid method employed the same procedure as for total nitrates, except that no oxidizing medium was introduced to convert lower valence products to the higher form. The results should afford some indication of the nitrates present and, by difference after oxidation, give a measure of the nitrites. It is believed that sufficient additional evidence is available to draw more positive conclusions regarding the composition of the mixture.

In our previous work we indicated that NO was probably present near the arc up to 40% but that not more than 12 to 17% of the mixture the animals breathed could be ascribed to this gas. We also showed the increased time factor leading to greater oxidation of the NO and consequent decrease of this gas. It is believed that the present results confirm these findings.

If we accept the usual statement that at the time of formation, neglecting numerous factors previously mentioned, the diazo reaction multiplied by 2 gives the combined NO_2 in the form of HNO_2 and HNO_3, we find that the theoretical volume of NO gas varies from 40% of the total immediately after welding and within 2 feet of the arc to about 25% 16 minutes after. At from 7 to 8 feet from the arc the amounts of NO calculated on the above assumption are from 15% immediately after welding to 10%, 16 minutes after welding. The values obtained while welding indicate that the largest amount of NO a short distance from the arc is 50% and that under the conditions of our experiments the largest amount of NO breathed by the animals was less than 20%. While these results obtained under the assumptions mentioned are somewhat higher than those indicated in our former experiments, it must be recalled that these assumptions have been previously criticized by us as leading to errors of various magnitudes. Furthermore these represent maximum quantities which were present for only a short time in the welding cycle. The amounts of unreacted NO the animals breathed over the whole experiment with coated rods was more nearly 12% of the total gas concentration reported as NO_2. The actual amount of unreacted NO may well be smaller than we have stated

TABLE 5

ANALYSIS OF NO_2 AS NITRATES AND NITRITES

All concentrations in p.p.m. NO_2, S. T. P.

SAMPLING TIME IN WELDING CIRCLE	ANALYZED AS				RATIO NITRATE / NITRITE (c)‡
	Nitrate	Nitrite (a)*	Nitrite (b)†	Nitrite (c)‡	
16 min. after 9:59 welding	11.88	2.97		4.58	2.6
	8.9		2.22	4.12	2.2
	14.86		2.96	3.67	4.0
Average.....	11.88	2.97	2.59	4.12	2.9
10 min. after 10:23 welding	19.38	2.98		5.53	3.5
	19.35		2.97	3.67	5.2
	26.79		2.97	5.97	4.5
Average.....	21.84	2.98	2.97	5.05	4.3
4 min. after 10:47 welding	22.53	9.01		6.50	3.5
	19.47		7.48	6.48	3.0
	26.95		5.98	6.46	4.1
Average.....	22.98	9.01	6.73	6.48	3.5
Immediately after 11:13 welding	31.83	3.03		7.10	4.5
	27.39		6.08	7.30	3.7
	21.27		7.58	6.56	3.2
Average.....	26.83	3.03	6.83	6.98	3.8
During 11:36 welding	18.06	3.00		3.79	4.6
	18.17		3.02	4.20	4.3
	15.09		4.52	3.72	4.1
Average.....	17.11	3.00	3.77	3.88	4.4

* Sulfanilic acid and a-naphthylamine.
† Brucine.
‡ Phenoldisulfonic acid less hydrogen peroxide.

TABLE 6

NO_2 CONCENTRATIONS IN P.P.M., S.T.P.

	8:30 A.M.	9:30 A.M.	10:30 A.M.	11:30 A.M.	12:30 P.M.	1:30 P.M.	2:30 P.M.
Immediately after welding.....	17	28	28	33	33	29	27
4 min. after welding.....	26	33	33	34	40	30	29
10 min. after welding.....	18	28	31	24	31	25	25
16 min. after welding.....	7	15	14	15	11	16	20
During welding...	13	30	26	28	20	20	27

as we have shown that the factors to be used when converting the diazo reaction representing HNO_2 to a true value of total NO_2 are quite variable, ranging from 1.7 to 5 or 6. We have merely attempted to set the top limits to the amounts of unreacted NO that could reasonably be expected in our experiments. The determination of total NO_2 gas appears to be the most regular factor and this is of aid in determining welding exposures (table 6).

exists when rods with differing coatings are employed in the welding process (4). The increased values of manganese are probably due to the Mn content of the coating. This explanation is also tenable in regard to the increased amounts of Fe_2O_3 but in addition changed physical and chemical conditions immediately about the arc may be significant.

As in the case of the bare rod no correlation is evident in the instance of the coated rod between the respective values of "nitrous gases" and metallic fumes (table 4). In addition there is such considerable variation from one type of rod to another that no exact conclusions can be reached.

TABLE 7

Fe_2O_3 AND MN CONCENTRATIONS

Mgm per cu. meter of air

	8:30 A.M.		9:30 A.M.		10:30 A.M.		11:30 A.M.		12:30 P.M.		1:30 P.M.		2:30 P.M.	
	Fe_2O_3	Mn	Fe_2O_3	Mn	Fe_2O_3	Mn	Fe_2O_3	Mn	Fe_2O_3	Mn	Fe_2O_3	Mn	Fe_2O_3	Mn
Immediately after welding	450	17	615	20	555	21	592	21	615	22	615	23	682	23
4 min. after welding	442	16	535	19	585	20	565	20	635	21	620	21	650	23
10 min. after welding	262	8	262	9	365	12	330	13	330	13	330	12	292	10
16 min. after welding	90	2	232	7	270	8	307	10	262	8	322	10	307	10
During welding	285	10	450	16	525	17	480	18	487	17	450	17	577	18

C. Metallic Fumes

The amount of iron fume obtained from the chamber air (table 7) ranged from 90 to 682 mg./cu.m. and 2 to 23 mg./cu. m. for the manganese. These quantities for both substances are considerably higher than in the case of bare rods—about twice as much Fe_2O_3 and ten times as much Mn were found. The average amount of manganese in the form Mn was about 16 mg./cu. m. with above 20 mg./cu. m. present for a considerable period of time. These results indicate that metallic fumes are considerably increased when coated rods are burned, even though some variation

When toxic agents are found, other than the gases usually associated with metallic arc welding, such as the manganese as reported for this rod, additional determinations other than NO_2 must be made if true exposure conditions are to be evaluated.

Table 1 includes the presence of SiO_2 and TiO_2 in appreciable quantities. Corresponding tests were made for the values of these substances in

e chamber fumes. In both instances standard laboratory methods ere applied (5, 6). Only traces of itanium were found in the samples air collected to determine the exosures of animals to various fumes. The only explanations are that the methods for titanium were not sensitive to the small quantities present, nd the fact that the impinger method id not collect the small size particles ($< 0.5\ \mu$) which comprised the larger art of the sample. This explanation is probably also true for the MgO and the CaO. The air borne samples collected with the electric precipitator for fumes alone gave the check results shown in table 1. We have reason to believe that most of the titanium is found in the welding slag.

Silica was found in quantities ranging from 19.6 mg./cu. m. to 97.5 mg./cu. m. The average value during the course of the experiment for 92 samples taken at various times in the welding cycle was 61 mg./cu. m. of air, calculated as SiO_2. The exact form in which silicon appears either in the rod coating or in the chamber fumes has not been investigated.

Further examinations were carried out for fluorides (7) and lead (8) but both of these substances were absent.

Animal Exposure Results

Rabbits and albino rats of both sexes were selected from our laboratory stock. A few purchased rabbits were distributed equally between control and exposed groups. There was little age variation; all rats, for example, were within 20 days of the same age. 24 rats were used in each of the exposed and control groups. 16 rabbits were exposed and the same number maintained as controls. Roentgen ray films were made of all animals at the beginning and end of this experiment. All animals were weighed weekly and subjected to the same diet, care and laboratory environment. Complete blood studies were made every 7 to 14 days of a representative portion of control and exposed animals. Animals were exposed for 6 hours daily, 5 days per week for a total of 46 days during an elapsed time of 65 days.

The exposure chamber temperature was taken at the beginning of each day of exposure, after 2, 4, and 6 hours. Relative humidity was measured less regularly, but in all there were 149 such determinations. The temperature averaged 85.3°F at the start of exposure. After 2 and 4 hours' operation of the chamber the temperature averages were respectively 90.0°F and 92.6°F, while the average temperature at the close of the exposure day was 92.6°F. For these same periods the exposure chamber temperatures exceeded those of the laboratory as follows: 6.9°, 8.3°, 9.7° and 9.5°F. Relative humidity values averaged 56% with 18 out of 149 below 50% and 6 above 70%. Ice was necessary in the chamber for cooling purposes since previous experience revealed that temperatures only slightly in excess of the maximum here reported were responsible for some animal deaths.

All experimental rabbits survived; one control died. 2 exposed rabbits lost an average of 5.5 ounces while 14 gained an average of 10.2 ounces; the average weight change was a gain of 9.6 ounces. The surviving control rabbits exhibited an average

weight gain of 12.9 ounces; two lost weight for an average of 3.4 ounces each while 13 gained an average of 14.3 ounces each.

3 exposed rats died, one after the first day of exposure, and the autopsy revealed no gross pathology. Another died after 22 days of exposure. The autopsy disclosed marked siderosis and multiple minute lung abscesses. The third died after 26 days but was not autopsied. The control rats all survived and gained weight for the duration of the experiment with an average of 32 gm. each. The exposed rats gained only an average of 2.9 gm., with 11 losing an average of 8.5 and 12 gaining an average of 13.5 gm.

1 rabbit and 2 rats were sacrificed for necropsy 3 days after exposure ceased and siderosis was found in all, but no significant gross pathology. 1 exposed rabbit died 5 weeks after exposure terminated and at autopsy presented siderosis and lobar pneumonitis. 10 exposed rabbits and 13 exposed rats were necropsied 6 weeks after exposure ended and gross examination revealed only siderosis; 1 rat presented multiple lung abscesses, and 3 revealed various degrees of atelectasis. 4 rabbits and 6 rats from the exposed groups, now in apparent full health, are maintained for any late pathologic developments.

7 weeks following the end of the experiment, 5 rabbit and 6 rat controls were sacrificed. Among these control rabbits no gross pathology was found. While the same was true of 3 rat controls, two revealed multiple lung abscesses and one showed atelectasis. Adequate tissues from representative animals have been preserved for microscopic inquiry.

Roentgen Examinations

The roentgenograms made before and after this experiment revealed no significant abnormalities. The films of rats included the entire animal while those of rabbits included the head, neck and thorax. The lung fields were available for study in all instances, as well as teeth and sufficient bony structures to detect likely metabolic changes due to the action of metals to the extent that such changes might occur in adult animals and be demonstrable radiographically. In three instances animals were rejected for the purpose of this experiment because of radiographic appearances which suggested lung abscesses. These animals were autopsied but no evidence of lung abscesses was found. Therefore, it is believed that interpretive errors are conservative. No roentgen findings from long-exposed animals have demonstrated any action of welding products.

Intraperitoneal Injections

4 groups of 6 rats each were used for peritoneal injections. 1 control group received physiological saline. Each of the three remaining groups were given injections of one of the following: (a) free silica; (b) ferric oxide; and (c) welding fume particulate matter collected by an electric precipitator. Suspensions of these dusts were prepared and injected according to established procedure (9, 10); albino rats (11) were substituted for guinea pigs.

Approximately 8 weeks after the intraperitoneal injections, these animals were sacrificed. The animals injected with physiological saline pre-

nted no abnormalities. Those in-cted with ferric oxide and welding me dust exhibited inert reactions. he group that received the silica spension all presented character-tic proliferative reactions.

Thus, the particulate matter com-rising "welding fume," which upon nalysis was found to contain about % of substance calculated as SiO_2, id not produce the peritoneal pro-iferative reaction characteristic of gnificant amount of free silica.

Migration of Iron Pigment in Lung Parenchyma

Previously it has been shown in xperimental animals that, after ex-osure to "welding fume" ceases, he iron pigment deposited in lung issue migrated through the lymphatics o the tracheobronchial nodes (12). Gardner has reviewed the mechanism provided for the removal of pigment from the air spaces of the lung and transportation of this material to the racheobronchial nodes. The peri-lymphatic and lymphoid tissue ac-cumulations of pigment particles are stated to be responsible for the macroscopic appearance of the lungs. To the extent that the gross appear-ance of pigmentation is due to lymph-oid tissue deposits and provided ade-quate lymph drainage exists, the gross pigmentation will decrease gradually after exposure ceases. We have been interested in ascertaining how com-plete this process is. Accordingly, 24 animals from previous exposures had been saved. From a group of animals having 25 days of exposure to welding fumes, 2 rats were autopsied 94 days after the last exposure, 1 rabbit after 104 days, 2 rats and 2 rabbits after 232 days, 2 rats and 1 rabbit after 1 year. Out of another group of animals having had 20 days' exposure, autopsies were performed on 1 rat 83 days after exposure, 4 rats and 5 rabbits 94 days after exposure, 1 rat and 1 rabbit after 232 days, and 1 rat and 1 rabbit after 336 days.

From examinations of this series of animals, it was found that in all instances tracheobronchial lymph nodes were pigment-laden but the distribution of pigment in lung tissue was much less dense and no longer lobular in outline. In some instances (animals examined 232 days to 1 year after exposure ceased) there were as few as 30 foci of pigmentation grossly visible in a single section of lung tissue. Complete elimination of gross iron pigment from welding fumes from the lungs of laboratory animals appears to be a reasonable expectancy.

Blood Studies

Complete cytologic studies and hemoglobin determinations were made on a representative number of exposed and control animals before, during and after the period of exposure. The cytology included the basophilic aggregation test and enumeration of erythrocytes and leucocytes. Differential leucocytic counts in all instances consisted of percentage determinations of polymorphonuclear neutrophils (segmented and non-segmented forms counted separately), small and large lymphocytes, monocytes, eosinophils and basophils. Hemoglobin values were obtained by an acid hematin method using Newcomer's standard disc in a B. & L. Duboscq colorimeter. The results of this work (111 complete blood counts including

hemoglobin determinations) reveal no significant changes in the formed elements of the blood. While there are some variations in hemoglobin these are not sufficient to warrant conclusions. This, as regards animals exposed to "nitrous gases" is in keeping with Lehmann's findings (14).

Methemoglobin

"Nitrous gases" have long been known to produce methemoglobin indirectly through the formation of nitrite compounds. This fact prompted a series of determinations for methemoglobin in exposed laboratory animals and practiced welders. Further impetus to this step came from Lehmann's observation (14) of "a considerable amount of methemoglobin" in one animal among a total of 20 animals used in his experiments.

For test purposes we adapted a modified spectroscopic method, using the Pulfrich-Zeiss photometer, for this analysis. The narrow absorption band at 630 μ is selected for use because the difference in transmittance between hemoglobin and methemoglobin is greatest at this point and the quantitative absorption of hemoglobin is small. The absorption band at 410 μ is not useful and that at 500 μ not as effective as the band at 630 μ.

The general procedure involves hemolizing the unknown blood by diluting a 0.1 ml. sample to 10 ml. with dilute ammonium hydroxide (1 ml. of concentrated NH_4OH per liter). Determine the transmittance of this hemolized blood at 630 μ and employ a similarly hemolized sample of "normal" (100% Hb) blood as reference. Consult the calibration curve and read direct the percentage concentration of methemoglobin in the unknown blood.

With the filters obtainable for use in the Pulfrich-Zeiss Photometer, the 630 μ band has a width of about 30 μ which is somewhat large but apparently satisfactory in practice, though it would be preferable to use an instrument having a slit grating and band width of 5 μ. To compensate for some of the errors involved we devised separate calibration curves for both male and female rats and rabbits. These calibration curves were obtained by preparing several hemolized blood solutions which were artificially adjusted to suitable known methemoglobin concentrations. The transmittance of each one was determined against a reference and the data plotted on semi-logarithmic paper.

Details of Calibration

Defibrinate "normal" (100%) blood of known hemoglobin concentration. Divide the sample into 2 parts and dilute one of these to 10 times its original volume with dilute ammonium hydroxide (1 ml. of concentrated NH_4OH per liter). Add to this diluted portion 3 drops of a freshly prepared 10% solution of potassium ferricyanide; this transforms all the hemoglobin to methemoglobin. Mix and make up to 100 times the volume of the original blood with the dilute ammonia to form solution (a). Dilute the remaining portion of the defibrinated blood to 100 times its original volume with the same dilute ammonia to form solution (b).

Prepare solutions (a1), (a2), (a3)

by diluting (a) with distilled water to concentrations of 70, 50 and 30%.

Prepare solutions (b1), (b2), (b3) by diluting (b) with distilled water to concentrations of 70, 50 and 30%.

Operating at 630 μ and 13 mm. solution depth, determine the transmittance of (a) with (b) as reference; (a1) with (b1) as reference, etc.

Form the calibration graph by plotting the determined transmittance values of the "a" solutions against the corresponding known methemoglobin contents of 100, 70, 50 and 30%.

The resulting series of solutions are equivalent to like concentrations of hemolized blood of the same methemoglobin content except that they do not contain the corresponding hemoglobin or cloudiness. It is necessary then to select as reference a hemolized "normal" blood similarly deficient in hemoglobin and cloudiness. Thus, if the artificial methemoglobin solution is, say, representative of 80% methemoglobin blood, it is 20% deficient in hemoglobin and consequently an 80% hemoglobin reference is necessary in its examination.

Experimental Results

Blood samples from 10 male and 11 female rats that had been exposed to welding fumes and gases in the coated rod experiments were taken at the end of the forty-third exposure day. The standard normal hemoglobin for a male and 2 female rats as well as the methemoglobin concentrations for these animals are shown in table 8. Methemoglobin concentrations ranging from 21.7 to 4.5% were found, with an average of 15% for the males and 11.2% for the females. 4 days after exposure had ceased the methemoglobin concen-

TABLE 8

METHEMOGLOBIN PERCENTAGES IN ANIMALS

(Standard hemoglobin for male and female rabbits, 84.1%. For male and female rats, 94.6% and 92.2% respectively.)

DAYS EXPOSED				DAYS AFTER EXPOSURE CEASED							
45 Rabbits		43 Rats		6 Rabbits		4 Rats		14 Rabbits		11 Rats	
M	F	M	F	M	F	M	F	M	F	M	F
3.5	4.5	21.7	15.4	2.5	0.6	2.7	0.6	0.5	0.1	4.3	3.1
2.0	0.9	17.5	8.0	3.1	1.3	1.5	2.7	5.5	0.2	3.5	2.1
4.8	2.1	10.4	12.0	3.5	0.7	2.5	0.6	1.7	0.1	1.9	2.5
1.3	5.5	14.7	5.5	1.5	0.5	4.2	0.3	0.3	0.1	2.5	2.4
1.0	3.5	11.5	9.5	3.5	0.3	3.8	0.6	0.0	0.4	1.5	1.5
3.2	1.3	16.0	17.3		0.1	4.2	4.2		0.2		3.3
	3.5	16.3	18.5		1.0	0.0	2.5		0.1	2.4	3.3
	2.5	10.4	18.0		0.1	0.7	2.3		0.5	3.6	2.7
	2.1	13.0	4.5		0.9	3.1	4.5		0.5	3.5	
	3.0	18.7	5.5		0.8	2.3	0.2		0.1	3.6	2.4
			12.6				3.1				1.9
Average 2.7	2.9	15.0	11.2	2.8	0.61	2.6	2.0	1.5	0.2	3.0	2.5

trations had dropped to a 2.6% average for the males and 2.0% for the females. This methemoglobin concentration was about the same 11 days after exposure had ceased. 16 controls showed a methemoglobin concentration average of 0.98%. This value of approximately 1% can be methemoglobin or error in the method. Assuming that this represents inherent errors, the rats 11 days after exposure would still have between 1 and 2% methemoglobin present according to the data presented. The appearance of high values of 4.2%

TABLE 9

METHEMOGLOBIN IN MALE RATS (BARE ROD WELDING)

BEFORE EXPOSURE	1 DAY EXPOSURE	3 DAY EXPOSURE	3 DAYS AFTER EXPOSURE CEASED	CONTROLS
%	%	%	%	%
0.5	2.4	2.3	0.0	0.5
2.0	3.8	2.4	0.0	0.0
0.6	3.0	3.5	0.0	1.5
0.0	2.1	3.1	0.0	1.8
0.0	1.0	3.6	0.1	
0.4	0.0	3.1	0.2	
Average 0.6	2.6	3.0	0.05	0.95

and 3.5% among the male rat controls and one value of 3.5% for one female rat control indicate a small amount of methemoglobin formed from unknown causes with some 1 to 2% of these values ascribable to error. These high values for methemoglobin were in such marked contrast to the majority of the rat controls that the above explanation seems necessary.

6 male and 10 female rabbits exposed for 45 days gave much lower methemoglobin percentages, the average for the males being 2.7% and the females 2.9% at the end of the exposure period. 6 days after exposure to welding fumes and gases ceased the males showed 2.8% and the females 0.6% methemoglobin. 14 days after exposure ceased the males' methemoglobin percentage dropped to 1.5% and that of the females to 0.2%. The animals used as controls furnished a general average of 0.6%. The data show that the rats' blood contained high percentages of methemoglobin after exposure to welding fumes and that this methemoglobin largely disappeared within 4 days. The rabbits' blood did not show a large amount of methemoglobin and the small amount found was largely dissipated within 1 week.

Since the animals in this experiment were exposed to somewhat less than 24 p.p.m. NO_2 and the animals in the bare rod experiments were subjected to about 70 p.p.m. NO_2, a 3-day exposure experiment duplicating the bare rod experiments was arranged. The average exposure was 70 p.p.m. As seen in table 9 the amount of methemoglobin increased gradually until the experiment stopped. 3 days after exposure ceased the methemoglobin dropped back to a negligible percentage. On the basis of these experiments it appears that significant percentages of methemoglobin are created in the blood of exposed laboratory rats whenever there are considerable concentrations of "nitrous gases" and that this methemoglobin readily appears within a few hours of exposure. These observations possibly are of some importance since the rabbit is known to be resistant to methemoglobin formation.

Inasmuch as our animals previously

ported on had been subjected to bout 70 p.p.m. of nitrous fumes spectively for 25 and 20 exposure lays, methemoglobin determinations ere made on those animals that had been saved. These determinations revealed no methemoglobin in the blood of any of the animals. It will be noted that none of our values were as large as those reported by MacQuiddy, Tollman, LaTowsky and Bayliss (13) in experiments with carbon arc burning where larger concentrations of "nitrous gases" were involved.

concentrations in the areas where these men worked did not exceed 13.3 p.p.m. in any case. A typical set of data is shown in table 10.

On the basis of the material presented it is believed that the determination of methemoglobin in workers exposed to "nitrous gases" will present some evidence of exposure to welding fumes. In the absence of other causes of methemoglobin formation the presence of any considerable quantity of this substance in an arc welder would suggest exposure. The same probably is true for gas welders.

TABLE 10

WELDER'S EXPOSURE

SAMPLE NO.	NO_2 S.T.P	REMARKS	METHEMOGLOBIN	
		Plant A		
	p.p.m.		%	
1	5.4	By welder's face (#1)	2.3	#1 welder
2	2.9	1 ft. from arc		
3	3.9	By welder's face (#2)	2.3	#2 welder
4	2.9	1 ft. from arc		
5	5.2	By welder's face (#3)	2.6	#3 welder
6	7.6	1 ft. from arc		
7	2.0	6 ft. from floor	2.5	Relief welder for the above
8	10.3	3 ft. from floor		
		Plant B		
1	4.6	By welder's face in direct path of fumes; 4 ft. from floor.		
2	10.6	Approx. 10" above arc in direct path of fumes; 5 ft. from floor.		
3	Trace	By welder's face; exhaust (canopy type) system appears to remove major part of smoke and fumes; 5 ft. from floor.		
4	7.6	Approx. 14" above arc; by welder's face in direct path of fumes; no exhaust; 5 ft. from floor.		
5	9.1	Welding at rear right corner inside of body; face high in path of smoke and fumes; 3 ft. from floor.		
6	0.0	Outdoors in open.		

Methemoglobin in Welders

Determinations of methemoglobin in a number of welders showed no values over 3% with the majority averaging 2.5%. The "nitrous gas"

COMMENT

From the foregoing results of animal exposures it may be agreed that formation of methemoglobin and

weight loss are the two significant findings. These two possibly are related but the extent of any relationship is not known.

Apart from methemoglobinemia, other exposure results should be considered in connection with animal weight changes. Roentgenographic examination of animals, chemical analysis of welding fume particulate matter, and intraperitoneal injection of this material all lead to the conclusion that the welding fumes contain too low a concentration of free silica to produce significant lung changes, or any concomitant growth disturbance. Presumably the weight loss is not caused by iron fume because earlier experiments provided exposures of significant amount of iron without comparable weight losses. No significant weight losses occurred among animals of earlier work on exposure to 3 times the concentration of NO_2 reported here.

Through this procedure of exclusion there remain only titanium and manganese to be considered in connection with growth retardation. In fact the limited observations made by us as to weight changes may not be associated with any particular substance related to arc welding. Of the two substances, titanium has little repute as a dangerous substance. Conversely manganese is a known toxic material with protean actions including that of promoting metabolic dysfunction. At this time, without any other proof, the disposition is to regard manganese as that welding material conclusively requiring further investigation.

It is tacitly accepted that the methemoglobinemia herein described results from "nitrous gases" and in percentages as low as 13. This may appear to be at variance with earlier statements that 70 p.p.m. NO_2 represents tolerable atmospheric conditions for prolonged periods. At present no literature discloses any harmful influence from methemoglobin when the percentage is of the order presented from our human and animal subjects.

The work of Lehmann and Hasegawa (14) from which stems most of the threshold standards widely accepted in this country and Europe, furnishes positive evidences only from quantities near to 70 p.p.m. and not from 39 p.p.m. as so often quoted. Certain anomalous interpretations of Lehmann's results cause us to cite direct statements in translation from an investigation carried out in part as long ago as 1907. At the same time mention will be made of other publications of the same general period not in keeping with the interpretations of Lehmann's studies.

The traditionally accepted "39 p.p.m." derives from a sentence in Lehmann's conclusions (not based on any published protocol data) stating that 0.1 mg. nitrous and nitric acid may be tolerated by many men for several hours and that 0.3 to 0.4 mg. always figured as total nitric acid appears to be directly dangerous. These authors state also that the danger point rises rapidly when doses of 0.6 to 1 mg. are given. It is not clear that these figures from nitrous and nitric acid may be associated directly with "nitrous gases" since the lowest concentrations of such gases investigated with animals (with negative results) was 0.19 mg. when calculated as total nitric acid. In

terms of p.p.m. of NO_2 this is the equivalent of 74 p.p.m. The lowest exposure in the three times that Hasegawa subjected himself to "nitrous gases" was 62 p.p.m. with negative or trivial consequences. A number of their individual experiments now are cited:

In animal experiment 1, 1 cat and 1 rabbit showed "no noteworthy symptoms" during the experiment or after 3 hours and no findings noted at autopsy. The concentration during this experiment was 0.19 mg. calculated as HNO_3 or 74 p.p.m. The next lowest concentration was in experiment 3 where 0.28 mg. calculated as HNO_3 or about 108 p.p.m. NO_2 was the exposure for 1 cat and no reaction or after-effects were noted at the autopsy 7 hours after the experiment started. Also in experiment 4, 1 rabbit showed no clear symptoms either during the experiment or at autopsy after being exposed to 0.42 mg. HNO_3 (163 p.p.m. NO_2) for 3 hours. The same results were found when another rabbit was exposed to 0.52 mg. HNO_3 (200 p.p.m. NO_2) for 1¼ hours. Their first conclusive results were obtained in experiments 6, 7 and 8 when a total of 3 cats were subjected to 0.56, 0.58 and 0.6 mg. HNO_3 respectively for 4¼, 5½ and 7½ hours. However they again record no symptoms in experiments 9 and 10 when a rabbit and a cat were exposed for 1 and 1 hour, 50 minutes respectively, each to 0.74 mg. HNO_3 (287 p.p.m. NO_2). No effects were clearly shown in regard to rabbits after 2 hours and 5 minutes when exposed to 9.66 mg.—a matter of several thousand p.p.m. of NO_2.

In Hasegawa's experiments on himself scant effects were noted from 62 p.p.m. though he reported irritation to the throat and thirst; no more actual difficulty reported after 60 minutes at from 75 to 100 p.p.m. and lesser concentrations for the next hour. Coughing, irritation of nose and throat, headache, vomiting, etc. were reported but no after-effects following a night of rest after exposure to 158 p.p.m.

However, Ronzani (15) who also did some animal work at about the same time found that 50 p.p.m. was without effect for the length of the experiment, 1 month. Ronzani found minimal effects in from 7 to 18 days with 100 p.p.m.

Yant (16) on the basis of a critical appraisal of the literature notes that there does not appear to be a logical correlation of response from increasing concentrations. Thus if 105 p.p.m. can be breathed for 6 hours without noticeable symptoms (17) and 105 to 210 p.p.m. is endurable for 30–60 minutes, why is 117–154 p.p.m. (14) hazardous even for a short exposure and 240–275 quickly fatal even for short exposures? Yant also points out that two publications (14, 18) quote 240–775 p.p.m. as quickly fatal even for short exposure while another notes (17) 240–275 p.p.m. for the same condition.

A further item of confusion appears in the German publication of Flury and Zernik (17) who credit the 39 p.p.m. figure to Henderson and Haggard (19) while the latter in their English work only ascribe that figure to Flury and Zernik's compatriots Lehmann and Hasegawa. Hess (17) could find no symptoms after 6 hours' human exposure to 105 p.p.m. Simi-

larly the U. S. Bureau of Mines often is quoted as the source of the much bandied "39 p.p.m." in its Technical Paper No. 248 (18). Actually this publication merely includes figures from the original Lehmann and Hasegawa paper as one item in a general table.

It should also be noted that Lehmann denies the chronic form of "nitrous gas" poisoning and this is important in removing apprehension concerning the cumulative effect of low concentrations of "nitrous gases."

Careful reading of some of these early publications indicates that these authors provided exposures of approximately 70 p.p.m. without injurious effects. Our work, instead of denying the accuracy of this preceding work, seems to confirm it.

Summary

This publication furnishes results on animals exposed to gases and fumes from arc welding with one coated electrode, in a 1000 cu. ft. experimental chamber. For 6 hours daily (5 days weekly) welding at one-half hour intervals (12 minute duration) was performed at 44 v. and 300–350 amp. To the gaseous and fumous welding products animals (rabbits and albino rats) were exposed 6 hours daily for 46 exposure days in a total of 65 days.

In addition to products created by the bare electrode, were the new items, silica and titanium. No results suggest any injury from either of these agents.

Contrary to findings from bare rods, growth rate disturbances were encountered, chiefly in rats for which the cause is unknown.

Substantial quantities of methemoglobin were found in the blood of rats. In our previous animal work, no determinations were made for methemoglobin. Casual repetition of bare rod experiments established prompt methemoglobinemia in rats on the first day of exposure. A limited number of production welders were examined at a time when the NO_2 concentration in the work place was only 13 p.p.m. Methemoglobinemia was established. It is possible that, in the absence of other sources of methemoglobin, the presence of this entity in the blood of welders may indicate exposure to nitrous gases.

The quantity of nitrous gases produced by uniform electric power in case of the one coated rod investigated is distinctly less than in the case of bare rods at the same power.

Metallic fume in the gassing chamber is substantially increased when coated rods are employed. This is notably true of manganese fume in the coated rod used.

As in the case of bare rod experiments in which high quantities of nitrous gases were evolved, no evidence whatever accrued relative to pulmonary edema, severe respiratory tract inflammation or similar findings, traditionally associated with nitrous gas action.

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in these days, the movements of industries to unusual places may likewise bring them unaccustomed diagnostic questions to answer.—*E. L. Middleton.*

INDUSTRIAL HYGIENE AND OCCUPATIONAL DISEASES. COURSE OUTLINE AND DIGEST OF LECTURES GIVEN IN COOPERATION WITH THE NATIONAL CONSERVATION BUREAU. *Paper. Mimeographed. Center for Safety Ed., Div. Gen. Ed., New York University, New York, 1941.*

This volume presents material of a course in industrial hygiene in 15 lectures given by various specialists: Dr. Greenburg gave the lecture on industrial dust, Dr. Lanza that on industrial health and prevention of occupational diseases, Dr. Patty on protective equipment, Mr. Stratton on air sampling and analyses, Dr. Schwartz on occupational dermatitis, Mr. Ficklen on toxic gases, etc. Each lecturer has given his story in a straightforward, well-condensed manner so that the collection makes an excellent primer for newcomers to the field. Besides the references given with each paper, there is a general bibliography for the whole field. The volume might profitably be given to industrial nurses and plant foremen as well as to student or practising physicians unfamiliar with industrial hygiene problems. —*Helen Lawson.*

CANCER AND OCCUPATION IN DENMARK 1935–1939. By *Johannes Clemmesen.* Translation by *Robert Fraser.* Paper. Pp. 75. NYT Nordisk Forlag-Arnold Busck, Copenhagen, 1941.

This study is based on the official records of the Danish National Health Service, which are known to be well kept. It was supported by the Danish Anti-Cancer League, which had 150,000 members. As the population of Denmark is about 3½ millions, approximately 1 person in 23 is a member of the Anti-Cancer League. First come discussions of earlier Danish cancer statistics, the character of the Danish death certificates and the regional distribution of cancer in Denmark. The yearly deaths from cancer during 1935–1939 were 140 per 100,000 of population. Then follow the classification of male "bread winners" in Denmark according to occupation, with tables and analytic diagrams of the cancer mortality of the different occupation and age groups, general as well as according to sites. The outstanding result of the work "is the low mortality from cancer in agriculture and the high mortality from that cause in industry, in the age group 45–64," which, as the author puts it, "very strongly suggests that also in Denmark [as in certain other countries] occupation has a bearing on the development of the malignant growths." The significance of these results with respect to prevention of cancer is emphasized and the need of comprehensive statistical studies of cancer, morbidity as well as mortality, in relation to occupation is urged. The normal conditions in Denmark would be especially favorable for the establishment of such a center. "At a first glance it may perhaps seem that this will be a very expensive way of proceeding, but in practice it will be a far shorter way to knowledge about human cancer than the untold costly experiments on animals that are going on the world over, while we neglect the registration of the great, unhappy experiment which nature itself is carrying out on our fellow man."—*J. A. M. A.*

THEORY OF OCCUPATIONAL THERAPY FOR STUDENTS AND NURSES. By *Norah A. Haworth and E. Mary MacDonald.* Cloth. Pp. 129. Williams & Wilkins Co., Baltimore, 1941 ($2.00).

This small volume will be a useful guide for persons interested in rehabilitation of ill or injured workmen. The title is misleading since there is little of theory in the book, but the practice of occupational therapy is considered in some detail and with a great many practical illustrations. Special kinds of work are suggested for various conditions (mental, cardiac, orthopedic, etc.) as well as work most suitable for men and for women. An appendix supplies illustrations of tools, looms and other equipment necessary in an occupational therapy department.—*Helen Lawson.*

VOLUME 23. INDEX TO TEXT AND BOOK REVIEWS

(Asterisk denotes book review)