4. The temporary failure of mobilization of bactericides in adrenaline-treated tissue appears to be the chief factor in the enhancement of infections by adrenaline. There is some evidence of an early removal of bacteria from the injection site which is retarded by adrenaline, with a consequent increase in the severity of the local lesion. The removal of certain vital dyes is also retarded by adrenaline.

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THE PATHOLOGY OF PHENYLDICHLOROARSINE POISONING IN RABBITS.

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PHENYLDICHLOROARSINE is a vesicant resembling lewisite in its general action. Application of large enough doses to the skin may result in death. With a view to establishing the major effects contributing to the lethal action of the vesicant and the way in which systemic poisoning is brought about, a microscopic examination of the various organs was carried out.

METHODS.

The rabbits used were of both sexes. Before applying the vesicant, an area on the back was freed from fur by clipping as closely as possible with scissors.

The phenyldichloroarsine (obtained from the Ministry of Supply) was redistilled *in vacuo* to give an almost colourless product. In several experiments the vesicant was measured from a micrometer-controlled syringe to the ground end of a glass rod and then applied to the skin. This method of application was reasonably accurate (error ± 10 per cent.), but was tedious and tended to spread the vesicant on the skin. Latterly, the "microburette" developed at Porton (Lane, 1947) was used exclusively and found entirely satisfactory. Tissues for microscopic examination were fixed in Bouin's fluid, and paraffin slices about 7μ in thickness were cut. In the majority of cases contrast staining was carried out with azo-carmine, aniline blue and orange-G. The haemalum-eosin method was used in a few cases. Bone-marrow was stained by the method of May, Grünwald and Giemsa.

RESULTS.

The dosage and the interval before killing the animal are shown in Table I.

TABLE I.—*The Dosage of Phenyldichloroarsine and Period before Death of Rabbit.*

Rabbit No.	Method of application.	Dose mg./kg.	Fate.
7	Microsyringe	3·0	Killed after 1 hour
8	,,	6·0	,, ,,
10	,,	6·0	,, 4 hours
11	,,	6·0	,, 24 hours
13	,,	3·0	,, 41 hours
14	,,	3·6	Died after 70 hours
17	,,	2·4	Killed after 7 days
18	,,	3·0	,, 9 days
23	Microburette	5·0	,, 3 days
24	,,	5·0	,, 24 hours
25	,,	5·0	Died after 5 days
26	,,	5·0	,, 40 hours
27	,,	10·0	,, 48 hours
28	,,	10·0	,, 40 hours
29	,,	3 × 4·6 within 24 hours	Killed 24 hours after first application
30	,,	5·0	Killed after 24 hours
31	,,	4·6	,, 24 hours

Skin.—In the contaminated area marked injury to the epidermis, corium and subcutaneous tissues was observed (Rabbits 7, 23, 25, 26 and 27). The initial change appeared to be coagulation necrosis, involving the epidermis and cutis in the centre, surrounded by a large area of subcutaneous oedema. In the necrotic patch there was damage to the capillaries, lymph space and probably nerve fibres.

The epidermis became loosened without significant blister formation, and the corium showed dilatation of the capillaries and immigration of leucocytes.

Least damage was seen in the hair follicles, which appeared to be resistant to the vesicant to some extent.

The skin changes set in after 1 hour (Rabbit 7) and reached a maximum in 2–3 days (Rabbits 23, 26 and 27). By the fifth day (Rabbit 25) there were signs of repair in the peripheral area. As usual, repair of the damaged epithelium progressed by epithelial proliferation, particularly from the hair follicles, and the repair of the corium by granulation of the connective tissue with fibrosis. The scab covering the necrotic area showed no tendency to separate during the first week of observation.

Circulatory system.—In all the tissues examined the capillaries were seen to have become dilated and more permeable, while some organs (lungs, liver, kidneys and adrenals) contained interstitial and parenchymatous haemorrhages, and certain serous surfaces and cavities showed widespread petechiae.

There were no detectable pathological changes in the myocardium (Rabbits 7, 8, 10, 14, 18, 23 to 29) or the walls of large blood vessels. Veins, however, were always much dilated and full of blood.

Respiratory tract and lungs.—The only lung changes seen after 1 and 4 hours (Rabbits 8 and 10) were active hyperaemia and haemorrhage. Pulmonary oedema (Rabbits 11, 24 and 29) was observed 24 hours after the application of the vesicant. After 40 to 48 hours hyperaemia, haemorrhages and oedema appeared not only in the lung (Rabbits 13, 26, 27 and 28) but also in the peribronchial tissue, the changes being most marked in lower parts of the cartilage-free bronchioles. Bronchioles were filled with oedema-like fluid and blood. The epithelium of the bronchioles began to show signs of degeneration and sloughed into the lumen. Changes similar to those in the bronchioles were seen in cartilaginous bronchii.

The hyperaemic areas of the lungs were filled with haemorrhages, the alveoli were partially destroyed, and a process of mild, diffuse inflammation was seen. Deposition of fibrin was not appreciable. Compensatory emphysema was noted around the oedematous areas, most marked near the margins of the lobule. The capillaries of the alveoli were tortuous and engorged with blood. There was accumulation of fluid in the interstitial tissue of the alveoli which also contained some leucocytes. The lumina of the alveoli contained fluid, desquamated epithelium and sometimes erythrocytes. Blood was seen in the alveoli when haemorrhagic inundation had occurred in the terminal bronchioles.

Veins in the lungs were much dilated and full of blood, and oedema was noted in the perivascular connective tissue.

After 3 days (Rabbit 14) to 5 days (Rabbit 25), the first signs of an inflammatory reaction became evident, resembling that seen in bronchopneumonia. The bronchioles and alveoli contained desquamated epithelium, fibrin, blood and a few mononuclear leucocytes. Hyperaemia was well marked. In contrast, in rabbit 23 absorption of oedematous fluid and a general picture of healing were seen 3 days after application of the vesicant. In Rabbit 18 no changes in the lungs could be observed after 9 days.

Duodenum, intestine.—Investigation of the digestive tract revealed no significant changes in any of the animals examined (Rabbits 7, 10, 11, 13, 14, 17, 23 to 29), except in that, as in other tissues, veins were dilated and full of blood.

Liver, bile-ducts, gall bladder.—Peribiliary hepatic necrosis (necrosis hepatis peribiliaris diffusa) was observed in all animals (Fig. 1 and 2). The changes

were well marked after 24 hours and were at a maximum 40–48 hours after contamination of the skin. Fatty infiltration was looked for, but was never appreciable.

After 1 hour (Rabbits 7 and 8) the sinusoids were enlarged and engorged with blood, but there was no distortion of the parenchyma or degeneration of liver cells. After 4 hours (Rabbit 10), hyperaemia was at a maximum and there was moderate oedema. Whole blocks of liver cells were seen to be segregated by enlarged, blood-filled capillaries or by accumulation of intercellular fluid (oedema). Some cells were vacuolated. Sinusoids and the portal and hepatic veins were much enlarged and packed with blood, and oedema was observed in the perivascular tissue. Distinct necrotic changes, situated in the periphery of the lobules close to damaged bile-ducts, were first seen after 24 hours (Rabbits 11, 24 and 29). Hyperaemia and oedema in the large bile-ducts and in the gall bladder were observed after 4 and 24 hours, and there were haemorrhages in the submucosa of the gall bladder. The epithelium in some bile-ducts and in the gall bladder began to show signs of the degeneration and desquamation after 24 hours.

The most obvious changes seen after 40 and 48 hours (Rabbits 13, 26, 27 and 28) were widespread focal necrosis situated at or originating from the periphery of the liver lobule Usually, when liver cells had been damaged, the nuclei had disappeared (karyolysis), but in some cases fragmentary or shrunk nuclei were observed (karyorrhexis or pyknosis). The cytoplasmic granules were not visible. The actual positions of destroyed cells could still be seen in the more resistant connective tissue framework. Sinusoids within and surrounding a focus of necrosis were considerably dilated and filled with blood. This appeared to be in part secondary to the shrinking of necrotic liver cells. The capillary plexus, branches of the portal vein, and sometimes the hepatic vein were much enlarged and packed with blood corpuscles. Thrombosis was often seen in branches of the portal vein, but seldom in branches of the hepatic vein. The endothelial cells of sinusoids and capillaries were practically normal, but in necrotic areas the stellate cells lining the lumina of sinusoids were reduced in number. Haemorrhages were evident around large and small bile-ducts. Bile-ducts within and around tissue lesions displayed in all cases well-marked damage, varying from epithelial degeneration to rupture of the walls or complete necrosis and disintegration. These changes occurred first in the peripheral, intralobular bile-ducts. Sometimes (e.g. Rabbit 27) primary degeneration and desquamation of the epithelium of interlobular ducts took place in the areas between quite undamaged liver lobules.

Within 3–5 days the foci of necrosis could still be recognized in the form of connective tissue scaffoldings where cells had been destroyed, but first signs of

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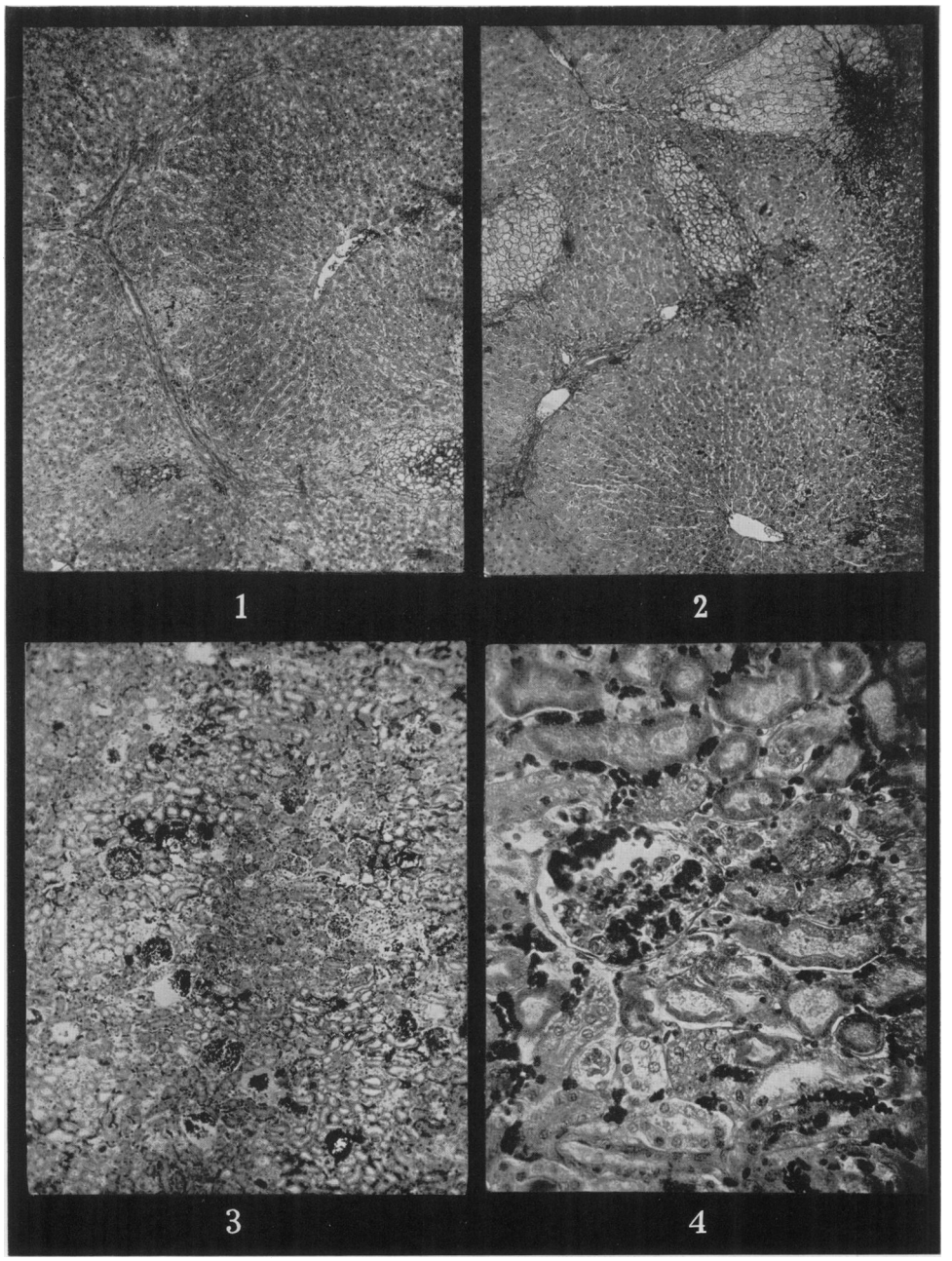
EXPLANATION OF PLATE.

FIG. 1.—Peribiliary hepatic necrosis. Rabbit 17, killed 7 days after 2·4 mg. of phenyldichloroarsine per kg. (× 48.)

FIG. 2.—Peribiliary hepatic necrosis. Rabbit 23, killed 3 days after 5 mg. of phenyldichloroarsine per kg. (× 48.)

FIG. 3.—Acute haemorrhagic nephritis and tubular damage in the cortex. Rabbit 14, died 3 days after 3 mg. of phenyldichloroarsine per kg. (× 48.)

FIG. 4.—Acute haemorrhagic nephritis and tubular damage in the cortex. Rabbit 14, died 3 days after 3 mg. of phenyldichloroarsine per kg. (× 240.)



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repair were evident (Rabbits 14, 23 and 25). Repair at this stage was mainly limited to proliferation of smaller bile-ducts and a fibroblast reaction, and occurred chiefly in Glisson's capsule which was markedly thickened and contained many new, small bile-ducts.

In Rabbit 17 which was killed 7 days after contamination of the skin the picture was similar, the reparative processes being particularly well-marked in the lobe to which was attached the gall bladder. The liver of Rabbit 18, killed 9 days after application of vesicant to the skin, showed no necrotic changes, although bile-duct proliferation associated with an interlobular fibroblast reaction was evident.

Kidney and ureters.—Histological changes in the kidney were more serious than was expected. Acute haemorrhagic glomerulo-nephritis was well-marked after 24 hours. After 40–48 hours, in addition to the glomerular changes, there was evidence of some tubular damage. In general, the picture appeared to be one of diffuse nephritis (Fig. 3 and 4). It seemed that damage to the renal tubules mainly involved the distal tubules in the cortex. There were no significant changes in the medulla of the kidney or in any of the ureters examined.

The kidney, apart from hyperaemia appeared normal 1 hour after contamination of the skin (Rabbits 7 and 8). At a period of 4 hours after poisoning (Rabbit 10), hyperaemia had increased and interstitial oedema could be observed. In another 20 hours, further to these changes, the first signs of glomerular damage became evident (Rabbits 11 and 24). After 40–48 hours from application (Rabbits 13, 26, 27 and 28) the most obvious change seen was the presence of fibrinous clots in the glomeruli with haemorrhages into the capsules and thence into the tubules. Disintegration of epithelial cells was well-marked. In the glomeruli, the haemorrhages and fibrin clots filled the capsule and thus obstructed the capillaries. Epithelial cells covering the capillary loops appeared to have been destroyed, and on occasion to have desquamated. The tubules (especially the second convoluted tubule), like the glomerular capsule, sometimes contained coagulated material (possibly albumen) and damaged epithelial cells. In the interstitial tissue there was marked accumulation of intercellular fluid (oedema), but no significant infiltration of white cells.

After 3 and 5 days (Rabbits 14, 23 and 25) hyperaemia was still considerable. The networks of capillaries surrounding convoluted tubules in the cortex were enlarged and packed with blood corpuscles. Also, but less frequently, the interwoven elongated capillaries in the medulla around the loops of Henle and the collecting tubules were affected. In Rabbit 23, under the capsule the venae stellatae connecting the renal and perirenal veins were enlarged and blood-filled. Three days after poisoning there became apparent a moderate degree of degenerative change in glomerular and tubular epithelium with haemorrhages and deposition of fibrin in the lumen of the capsule and the tubule.

In Rabbit 17, killed 7 days after the administration of the vesicant, there were small anaemic infarcts in the renal cortex (as well as infarctions of the adrenal cortex), resulting from the presence of an embolus in a branch of an artery, which in its turn penetrated the cortex. The infarctic mass had become dense, but the outlines of cells and even of nuclei could be made out quite clearly, except where glomeruli were completely necrosed and tubules had been totally destroyed and had collapsed. In the area of the lesion, where tubules had collapsed there

was compensatory enlargement of neighbouring tubules. Interstitial connective tissue showed a fibroblast reaction in this region.

Bone-marrow, spleen, lymph nodes.—Investigation of the red bone-marrow of two poisoned rabbits (30 and 31) revealed no significant changes other than small haemorrhages.

In two spleens examined (Rabbits 11 and 23) there appeared to be some damage to the malpighian corpuscles. Large mononuclear endothelial cells containing phagocytozed fragments of nuclear debris (lymphorrhexis) were seen in place of small leucocytes in nodules of lymphoid tissue. There were no significant changes in the splenic pulp or its cells. The endothelial mononuclear cells contained erythrocytes in various stages of disintegration.

Apart from marked oedema, no changes were seen in lymph nodes (Rabbits 26 and 27).

The histological picture made it clear that the cells of the reticulo-endothelial system (in the more exact sense, i.e. comprising endothelial cells of the spleen, certain branched cells in the bone-marrow, the stellate cells of Browicz-Kuppfer and the reticulum cells of the lymph nodes) were more resistant to the effects of phenyldichloroarsine poisoning than other cells.

Hypophysis, thyroid, parathyroids and adrenals.—The hypophysis (Rabbits 7, 24, 25, 27 and 28), thyroid and parathyroids (Rabbits 10, 23, 24 and 25) showed no changes apart from marked congestion.

The most characteristic alterations in the adrenals (Rabbits 7, 8, 10, 11, 17, 18, 23 to 28) were great congestion and haemorrhage. Blocks of partially damaged cells with pyknotic nuclei were separated by enlarged, blood-filled capillaries and accumulation of extracellular fluid. Occasionally, small thrombi could be seen. The intercolumnar spaces between the fascicular bundles were greatly dilated. Destruction of cells in the zona glomerulosa under the capsule was sometimes observed, and in one case (Rabbit 28), this had developed so far that foci of necrosis were present, in which even the outlines of cells had disappeared, leaving visible only outlines of nuclei in densely packed masses. Since the rabbit had died under the action of the vesicant these changes may have represented post-mortal autolysis. In some cases (e.g. Rabbit 17), infarctions of the adrenal cortex occurred in the area of the middle zona fasciculata. These did not extend to the outer zona glomerulosa and were clearly separated from neighbouring fascicular bundles. In the infarctic area, cells were partially necrosed, the network of vacuoles in the cytoplasm normally seen after fixation of sections having disappeared along with some nuclei. Outlines of the damaged cells and as a rule of the nuclei, could, however, be clearly seen.

DISCUSSION.

Many of the rabbits used in this work were examined for distribution and excretion of arsenic by Storey (1943) employing the method for arsenic determination of Levvy (1943). Interpretation of the results was complicated by the rather incomplete absorption from the skin found by Graham, Levvy and Chance (1947), but if allowance be made for this factor, the distribution figures resembled in many respects those for phenylarsenoxide (Chance, Crawford and Levvy, 1945),

the hydrolysis product of phenyldichloroarsine especially in the large and rapid uptake of arsenic by blood cells and lungs. Liver and kidney also showed high arsenic concentrations. In the case of phenyldichloroarsine, however, excretion of arsenic took place to approximately the same extent in urine and faeces, a total of about 2 per cent of the dose applied to the skin being cleared daily. The amounts of arsenic excreted during the first two days were no greater than at any other period, suggesting that absorbed arsenic was rapidly fixed in the tissues, from which it was released at a slow and steady rate. It may be noted that, although the concentration of arsenic in striated muscle was comparatively low, this tissue probably contained the greater part of the arsenic in the body, since it comprises nearly 50 per cent of the body weight of the rabbit.

The data for distribution and excretion of arsenic reflect the pathological changes observed. Since the necrosis at the site of contamination occupied only a small area of skin in these experiments, the local changes cannot be regarded as having contributed seriously to death. On the other hand, the central area of necrosis was surrounded by subcutaneous oedema over a very large area, the location of which seemed to be determined by gravity.

The more severe effects produced by phenyldichloroarsine appeared in general to result from the systemic action of the arsenic on the capillaries with consequent fluid loss from the circulation, and secondary damage which was mainly restricted to the lungs, liver and kidneys. In addition to secondary effects due to circulatory disturbance there appeared to be direct injury of certain organs, particularly the liver and kidneys.

After a period of 1–4 hours following the application of vesicant to the skin the capillaries throughout the body were seen to have become dilated. Numerous capillary haemorrhages, thrombosis, embolism and sometimes infarction were observed. The general picture of capillary paralysis with enormous accumulation of plasma in tissues, especially in the subcutaneous tissues and lungs, suggested that death at an early stage, i.e. 24–48 hours after contamination, was due to a shock-like condition, resembling that found by Cameron, Courtice and Short (1947) for lewisite poisoning.

The damage to the lungs (congestion and oedema) resulted mainly from disturbances in the circulation. Although foci of oedema were well-marked after 24 hours, there was no massive oedema such as is seen in phosgene poisoning. After 3–5 days the congestion and oedema disappeared or were followed by septic or aseptic complications.

The general picture of liver damage was one of necrosis in the periphery of lobules, close to damaged bile-ducts. The endothelium of the dilated and blood-filled sinusoids and the stellate cells seemed to escape injury. A clear-cut distinction cannot readily be made between the effects arising from disturbance of the circulation and those caused by a direct action of an arsenic derivative on the liver cells. It does not seem possible, however, that changes in the blood supply to liver cells (anaemic necrosis) could have been entirely responsible for the wholesale destruction which appeared at an early stage of poisoning. It seemed that peripheral necrotic damage of liver cells may have been associated with either changes in neighbouring sinusoids (distribution of arsenic derivatives *via* the blood stream) or in bile-ducts (excretion of arsenic derivatives). It has been shown that poisoned rabbits excrete as much arsenic in the faeces as in the

urine. Excretion in bile was not investigated by Storey, but the fact that there are no significant changes in the intestinal mucosa supports the view that arsenic in the faeces is excreted in the bile. It is not considered that the liver damage was sufficiently extensive at any time during the period studied (up to 9 days after contamination) to be itself a cause of the deaths seen in phenyldichloroarsine poisoning in rabbits.

In the case of kidney, it was again difficult to distinguish effects secondary to circulatory changes from direct damage to the renal cells. During the period of acute poisoning (4–24 hours) the effects of general and local capillary damage predominated. The oliguria, haematuria or even anuria regularly observed in the early stages of poisoning can be regarded as resulting from the shock condition (diminution in plasma volume, fall in blood pressure and, consequently reduction in glomerular pressure and glomerular filtration). In later stages (after 24–40 hours) it seemed that oliguria may have been due in part to direct damage of glomerular epithelium. The pathological changes were reminiscent of those seen in other forms of acute (haemorrhagic) glomerular nephritis. The blocking of the glomeruli with fused masses of erythrocytes and desquamated epithelial cells was sufficient to have caused diminution of urine filtration. Some tubular damage first appearing 24–40 hours after contamination was also probably in part due to direct poisoning, and may indicate that the distal tubules either actively excreted the arsenical in the blood or, alternatively, reabsorbed the toxic compound after it had passed through the glomeruli.

Changes observed in the adrenals (hyperaemia, haemorrhages, infarction) could all have arisen entirely from circulatory disturbances. It seems that the shock-like condition produced by phenyldichloroarsine was not secondary to damage of the adrenal cortex of the animals examined. In fact, one rabbit (17) was in good condition when killed 7 days after poisoning, although serious haemorrhagic infarction of the adrenal cortex had occurred.

The myocardium, digestive tract, bone-marrow, lymph nodes, hypophysis, thyroid and parathyroids showed no changes, apart from disturbances of the circulation. In the spleen, some lymphorrhexis was seen, suggesting that the toxic agent acted directly on this organ.

It is interesting to compare the changes caused by phenyldichloroarsine with the effects produced in animals by toxic doses of lewisite (Cameron, Courtice and Short, 1947) and therapeutic arsenicals, such as arsphenamine, neoarsphenamine, atoxyl and mapharsen (Petri, 1930; Gruhzit, 1934). All the compounds mentioned resemble phenyldichloroarsine in that they produce congestion, haemorrhages and other circulatory disturbances in all organs during the first 24 hours of poisoning.

The pathological changes seen with phenyldichloroarsine do not appear to differ from those observed in rabbits treated with lewisite, except in that the kidney damage may have been more severe in experiments with phenyldichloroarsine than has been described for lewisite. Phenyldichloroarsine, like atoxyl and mapharsen, produces much more serious kidney damage than is seen with arsphenamines (arsenobenzenes). Mapharsen is exceptional in that it affects the liver much less seriously than the other compounds under discussion. In general, all the therapeutic arsenicals act on other organs, such as the lungs, spleen and adrenals, in much the same way as phenyldichloroarsine. It thus

appears that the systemic changes produced by arsenical vesicants do not differ radically from those found with non-vesicant, organic, arsenic compounds.

After phenyldichloroarsine no perceptible injury to the tissue cells of bone-marrow has been observed. Bone-marrow changes have been seen in man and in experimental animals after repeated administration of arsphenamines. It should be borne in mind, however, that in the studies with phenyldichloroarsine the toxic agent was administered in a single dose.

SUMMARY.

1. After application of phenyldichloroarsine to the skin of rabbits, damage to the capillaries, and haemorrhages sufficiently severe to cause shock or early death, were seen all over the body, the effects being most pronounced in lung.

2. The histological pictures suggested that direct poisoning of liver and kidney occurred.

3. It was not considered that the liver and kidney damage was sufficiently extensive at any time during the period studied to be in itself a cause of the deaths seen in phenyldichloroarsine poisoning.

This investigation formed part of a research programme carried out for the Ministry of Supply under the direction of Dr. G. A. Levvy and a preliminary account of the work was given limited circulation by the Ministry in 1943.

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