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TOXICOLOGY OF ALDRIN IN RATS+*

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Abstract : Aldrin-mixed diet, fed to Sprague Dawley rats at a dose of 20 mg, 8 mg and 2.5mg/kg body wt./day for 48 hours, 15 days, and 18 months, respectively produced significant changes in the blood and liver. The haemoglobin content, red blood cell count and packed cell volume decreased, while the white blood cell count increased under all treatments. The serum glutamate oxaloacetate transaminase (GOT), alkaline phosphatase (AP) and isocitrate dehydrogenase increased 370, 141 and 135%, respectively in 48 hour treatment. The creatin phosphokinase activity increased (83%) in 15 day treatment. The acid phosphatase activity increased 97% after 6 months treatment. Bilirubin content increased in 15 day, urea in 15 day and 18 month and protein content under all experimental conditions. Cholesterol and free amino acids (FAA) contents decreased after aldrin feeding. In 48 hour experiment hyperglycemia was induced, while hypoglycemia was found in 15 day treatmant.

In liver, AP and GOT activities increased 171% and 28% respectively in 48 hour feeding, while lactic dehydrogenase (LDH) decreased (26%). In 15 day feeding experiment the glutamate pyruvate transaminase (GPT) and LDH activities increased 186% and 23% after 9 and 15 days, respectively. This increase was more pronounced in 18 months treatment. The hepatic cholesterol generally decreased in 48 hour and 15 day treatments. The FAA and glucose contents decreased in 48 hour and 6 month treatments, while in 15 day feeding reverse pattern was obtained. Hepatic soluble proteins increased in 48 hour and 18 month feeding groups, DNA content remained unaltered, while RNA showed almost constant increase in 15 day treatment. Aldrin treatment produced hypertrophy of hepatic cells, nuclei and nucleoli. Fatty degeneration and extensive vacuolation was evident in 48 hour feeding. The vacuolation, granulation of hepatic tissue and prominent clear areas around nuclei were found in 15 day feeding. These changes, with distorted nuclei and enlarged kupffer cells, were also observed in 18 months feeding group.

Key Words : Aldrin, liver function tests, chemical composition of liver, haematology, Sprague Dawley rats, histopathology of liver, chlorinated insecticides.

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INTRODUCTION

Aldrin is a chlorinated compound of cyclodiene group. It is one of the most active, general contact and stomach insecticide and has been used against the crop pests and termites in the soil (Hassall, 1969; Korschgen, 1970, 1971 ; Lichtenstein *et al.*, 1970; Trivedi and Srivastava, 1986 ; Ahi, 1988; Yao *et al.*, 1988). Like other compounds of the group, aldrin is highly lipophilic (Siddiqui and Saxena, 1985) and is a central nervous system stimulant (Agarwal *et al.*, 1988; Chandra and Podder, 1988). Aldrin is readily converted into its epoxide, dieldrin, in the soil and biological system such as fat, muscle, liver and blood (Bann *et al.*, 1956 : Buck and Van, 1968 ; Lichtenstein *et al.*, 1970 ; Korschgen, 1971 ; Corbett, 1974 ; Ghiasuddin and Menzer, 1976 ; Kurihara *et al.*, 1984 ; Lang *et al.*, 1986; Dhanaraj *et al.*, 1989) where it is stored almost unchanged. However, Akkermans *et al.* (1973) has stated that dieldrin may be metabolized first to aldrin-transdiol before it can exert its neurotoxic action.

Kaphalia and Seth (1984) and Mick *et al.* (1971) have shown the presence of aldrin residues in the blood of food animals, chicken and human beings. Kan (1978) has also published a review regarding the accumulation of these pesticides in poultry. Remarkable amount of residues are reported from the plants and food stuffs (Correia, 1972 ; IARC, 1973 ; Balayannis, 1974; Celeste *et al.*, 1988 ; Kahunyo *et al.*, 1988). In literature several cases regarding contamination of aquatic and terrestrial food chains with insecticide residues are quoted (Graham, 1970; Korschgen, 1970; Rudd, 1975 ; Hashemy-Tonkabony and Langaroodi, 1976 ; Cathey, 1982 ; Juneja and Mahajan, 1984; Hamilton, 1985; Al-Omar, 1986 ; Kumar *et al.*, 1988; Dhanaraj *et al.*, 1989) Its residues were also reported from the air (Wallace and Sherren, 1986). Deichmann *et al.* (1971a) fed aldrin to pure-bred beagles for 10 months which resulted in a constantly increasing concentrations of dieldrin in blood and body fat. Discontinuation of aldrin administration resulted in the gradual decline in dieldrin fat concentrations from 75 ppm to 25 ppm after 12 additional months.

These residues pose a severe threat to our ecosystem because of their greater stability (Hamilton, 1985). They are very slowly metabolized and excreted by mammalian system in milk and urine or stored in different dairy products (Buck and Van, 1968 ; Downey *et al.*, 1975 ; Vreman *et al.*, 1976 ;

Kodric-Smit *et al.*, 1980 ; Siddiqui and Saxena, 1985). As far as vertebrates are concerned, aldrin is a highly toxic compound (Truhant *et al.*, 1974 ; Verma *et al.*, 1978 ; Singh and Singh, 1982 ; Srivastava *et al.*, 1989). The toxicity may be due to direct ingestion through food, inhalation and industrial and occupational exposure, for example, during agriculture and public health programmes. Hayes (1963) has reported that the effects of aldrin and dieldrin are almost similar, both qualitatively and quantitatively in animals and appeared to be true in man also. Cleveland (1966) did not observe any mortality or decrease in growth rate in rats after feeding aldrin-mixed diet for 2 years at the concentrations of 2.5, 12.5 and 25 ppm. However, at 12.5 and 25 ppm dose, the animals showed increased liver weights.

Aldrin affects the blood components (*e.g.* Moss and Hathway, 1964 ; Deichmann *et al.*, 1971 ; Mick *et al.*, 1971 ; Mahajan and Juneja, 1979 ; Srivastava and singh, 1981 ; Verma *et al.*, 1987 ; Srivastava and Srivastava, 1988) as it is the first target and carrier of insecticide inside the liver and other tissues of vertebrates (Hamilton., 1985). There are scattered reports regarding the effect of aldrin on biochemical aspects of vertebrates, including enzymes (Rodrigues and Puga, 1979; Verma *et al.*, 1980 ; Enan *et al.*, 1982; Mahajan and Sharma, 1984 ; Denison and Yarbrough, 1985 ; Chatterjee *et al.*, 1988 a, b,c). However, several reports are available from this laboratory in connection with the biochemical pathology induced by different pesticides on the blood and liver of various mammals (Ali and Shakoori, 1981, 1988 a,b; Shakoori and Ali, 1985 ; Shakoori *et al.*, 1982, 1984 ; Shakoori and Haq, 1987 a,b). Gertig *et al.* (1971 a,b) have reported the effect of aldrin on transaminase (aspartate aminotransferase and alanine aminotransferase) and phosphatase (alkaline and acid) activities. Aldrin, like other xenobiotics, also induce microsomal enzymes (Bellward *et al.*, 1975 ; Burns, 1976 ; Vainio and Parkki, 1976 ; Stevens *et al.*, 1977 ; Singh *et al.*, 1985) the extent of which, according to Krample and Hladka (1975), is dose-dependent.

Aldrin also affects the carbohydrate metabolism in different animals (Srivastava and Singh, 1981 ; Gupta and Dhillon, 1983 ; Omkar *et al.*, 1984 ; Gluth and Hanke, 1985). Presence of aldrin in human placenta, fetus and its accompanying fluids was reported by Saxena *et al.* (1980, 1981) and Siddiqui and Saxena (1985). Transplacental movement of aldrin in Egyptian buffaloes

was studied by Aly and Fassbender (1984) and was also found in fetal tissues. Reproductive function and development in animals is also altered by aldrin (Kitselman, 1953 ; Deichmann *et al.*, 1971 b ; Ottolenghi *et al* ., 1973 ; Singh and Singh, 1982 ; Crawford and Guarino, 1985 ; Chatterjee *et al.*, 1988 a,b,c ; Gonzalez and Hiraldo, 1988), besides known neurotoxic effects (Gupta, 1975 ; Srivastava *et al.*, 1989). Bone growth abnormalities in goats during chronic aldrin intoxication was shown by Singh and Jha (1982). Recently an inhibition of metabolic coordination was reported through its effects on gap-junction communication (Lin *et al.*, 1986). Aldrin has also been shown to affect the course of cardiac processes in rats and rabbits (Kagan *et al.*, 1974).

Exposure of animals to aldrin resulted in histopathological changes in liver, kidney and other tissues, which include parenchymatous cell degeneration, hypertrophy and necrosis (Kitselman, 1953 ; Cleveland, 1966 ; Reuber, 1976, 1980 ; Mathur *et al.*, 1981 ; Bernardi *et al.*, 1988). Correlations between accumulation of organochlorine insecticides and pathologies of liver, carcinoma, premature birth, lung cancer, leukemia, malignant neoplasia, aplastic anemia, atrophy of the bone marrow and kidney diseases have been made (Vrochinskii *et al.*, 1976 ; Reuber, 1975, 1976, 1977, 1980 ; Singh *et al.*, 1985).

There are conflicting reports about the carcinogenic potential of aldrin in the literature (for example, Cleveland, 1966 ; David, 1979 ; Reuber, 1976, 1980). However, National Cancer Institute (NCI) report (1978) concluded that there was no convincing evidence that aldrin or dieldrin were carcinogenic, although increase in liver lesions called hepatoma were observed in mice. This report is based on the previous work of Davis and Fitzhugh (1962), Fitzugh *et al.* (1964), Song and Harville (1964), Cleveland (1968), Walker *et al.* (1968), Thorpe and Walker (1973), Stevenson *et al.* (1976) and Deichmann and MacDonald, (1977). Gillespie *et al.* (1979) have made an assessment of carcinogenic risks in the United States and Great Britain due to aldrin and dieldrin.

The present studies aim at evaluating the effect of short and long term feeding of aldrin to rats. These effects have been assessed in terms of haematological, biochemical and histopathological changes in blood and liver of aldrin treated rats.

MATERIALS AND METHODS

Animals and their maintenance

Sprague Dawley albino rats raised in the Animal House of the Department of Zoology, were used for the present studies. For short term experiments, two groups of female rats, with average weight 181.51±8.98g and 6-8 months of age were used. One group was used for feeding insecticide for 48 hours, while the second was used for feeding insecticide for 15 days. For long term experiments, male rats (135.38±19.41g average weight) of 2-4 months of age were used.

The rats were fed on a feed which was prepared by the formula mentioned in Ali and Shakoori (1988a).

Insecticide used and its administration

Aldrin [(1R, 4S, 5S, 8R)—1, 2, 3, 4, 10, 10—hexachloro—1, 4, 4a, 5, 8, 8a—hexahydro—1, 4, 5, 8—dimethanonaphthalene], a chlorinated insecticide of cyclodiene group (20 EC) was obtained from Entomology Department, University of Agriculture, Faisalabad, and administered to the animals orally alongwith feed as strong and weak doses.

For short term experiments, two levels of strong doses were administered. In one group of rats a strong dose of 20 mg (0.4 LD_{50}) aldrin/kg body weight/day was administered for a total period of 48 hours. In the second group, 8 mg (0.16 LD_{50}) aldrin/kg body weight/day was administered for a total period of 15 days. A weak dose at a rate of 2.5 mg/kg body weight/day (0.05 LD_{50}) was administered to another group of rats for 18 months.

The insecticide-mixed diet for 48 hour experiment was prepared by mixing 0.8 ml of 20% EC aldrin in 1 kg of rat feed. Since each experimental rat, on the average, consumed 30 g of feed daily, it will get 20 mg (a.i.) aldrin/kg body weight/day. For 15 day experiment, 0.32 ml of 20% EC aldrin was mixed in 1 kg of rat feed. The rats in this way got 8 mg (a.i.) aldrin/kg body weight/day. For long term experiment, the insecticide-mixed diet was prepared by adding 0.1 ml of 20% EC aldrin in small amount of water and then that insecticide-contained water was thoroughly mixed with 1 kg of rat feed. That way the rats consumed 2.5 mg aldrin (a.i.)/kg body weight/day.

Experimental procedure

Two short term experiments were set up. For the first, 8 animals were fed on aldrin mixed diet, prepared for this purpose for 48 hours. A group of 4 rats were weighed, anaesthetized and slaughtered every 24 hours. The blood samples were collected and livers taken out, weighed and processed for various analyses. Eight control rats were processed exactly in the same manner, except for the aldrin treatment. For the second short term experiment a group of 20 rats were initially fed on aldrin mixed diet regularly for a total period of 15 days. A group of four rats were weighed, anaesthetized and slaughtered regularly every third day. The blood samples were collected and livers taken out, weighed and processed for various analyses. A group of control animals was proceeded exactly in the same manner except for the aldrin treatment. For long term study, a group of 12 animals was fed regularly on aldrin mixed diet, prepared for this purpose, for a total period of 18 months. Every six months 3-4 rats were weighed, anaesthetized and slaughtered. Their blood samples and livers were collected and processed as mentioned in the short term experiment. Three groups of rats, each of 4-6 animals, fed on aldrin free diet, were slaughtered each time and used as control of the long term experiment.

Collection of blood

Blood specimens were collected from the inferior vena cava with the help of 10 ml sterilized syringe and transferred gently to a blood centrifuge tube after removing the needles from the syringe. It was allowed to clot and centrifuged at 800 g to obtain a clear serum which was, afterwards used for different biochemical studies. Small quantity of blood was collected in the tube containing EDTA as an anticoagulant and was used for various haematological studies. The amount of EDTA used was 2 mg/ml of blood, and it was mixed gently by rotation of tube.

Liver processing

The liver was taken out, weighed and then processed for histological and biochemical studies. Liver weight, alongwith body weight was used for calculating relative liver weight (RLW ; liver weight/ body weight × 100).

Saline extract was prepared by homogenizing a piece of liver in 0.89 % saline in a motor driven glass homogenizer. The homogienate was

centrifuged at 8500 g to obtain clear supernatant, which was then used for different biochemical studies. A portion of liver was weighed and processed for the estimation of nucleic acids (DNA and RNA) and total protein content. For cholesterol estimation, ethanol extract was prepared. A small piece of liver was also fixed in Bouin's fixative for histological studies.

Hamatological studies.

Anticoagulant (EDTA) containing blood was used for studies which involved the estimation of haemoglobin (Hb) content according to Van-Kampan and Zijlstra (1961), packed cell volume (PCV) according to micro-haematocrit method of Strumia *et al.* (1954) and total erythrocytic count (TEC) and total leukocytic count (TLC) according to routine clinical methods. The data obtained was then utilized for calculating different haematological indices *i.e.* mean cropuscular haemoglobin (MCH), mean corpuscular volume (MCV) and mean corpuscular haemoglobin concentration (MCHC) according to Dacie and Lewis (1977).

Biochemical analysis of blood

The analysis of blood serum was carried out for evaluating liver dysfunctioning and other metabolic disorders which involved the estimation of acid phosphatase (AcP ; orthophosphoric monoester phosphohydrolase, acid optimum ; EC. 3.1.3.2) and alkaline phosphatase (AP ; orthophosphoric monoester phosphohydrolase, alkaline optimum ; EC. 3.1.3.1.) activities according to Kind and King (1954), amylase (1,4-glucan, 4-glucano-hydrolase; EC. 3.2.1.1) activity according to Wootton and Freeman (1982), cholinesterase (ChE; acylcholine acyl-hydrolase; EC. 3.1.1.8.) activity according to Rappaport *et al.* (1959), creatine phosphokinase (CPK; ATP : creatine N-phosphotransferase; EC. 3.7.3.2) activity according to Okinaka *et al.* (1961), isocirate dehydrogenase (ICDH; threo-Ds-isocitrate : $NADP^+$ oxidoreductase; EC. 1.1.1.42) activity according to Bell and Baron (1960), lactate dehydrogenase (LDH ; L-lactate: NAD^+ oxidoreductase ; EC. 1.1.1.27) activity according to Cabaud and Wroblewski (1958), serum glutamate oxaloacetate transaminase (SGOT; L-aspartate 2-oxoglutarate aminotransferase; EC. 2.6.1.1.) and serum glutamate pyruvate transaminase (SGPT ; L-alanine 2-oxoglutarate aminotransferase ; EC. 2.6.1.2) activities according to Reitman and Frankel (1957). A brief account of the reaction mixtures with respect to each enzyme is given below.

Amylase activity : One milliliter of 0.4 g/l buffered starch, pH 7.0 was mixed with 0.1 ml of 10 fold diluted serum in 0.15 M saline. The mixture was incubated at 37°C for 15 minutes. The reaction was stopped and colour was developed by the addition of 0.4 ml of 0.01 N iodine solution. The absorbance of blue colour solution of test and control was measured at 660 nm wavelength after dilution with water.

AP activity : One milliliter of carbonate buffer, pH 10.0, 1 ml of 0.01 M disodium phenylphosphate and 0.1 ml of serum were incubated for 15 minutes. The reaction was stopped with 0.8 ml of 0.5 M NaOH followed by the addition of 1.2 ml of 0.5 M $NaHCO_3$, 1 ml of 4-aminoantipyrine (0.6%) and 1 ml of potassium ferricyanide (2.4%). Reddish brown colour was read at 510 nm wavelength. Crystalline phenol (1 mg/100ml) was used as a standard.

AcP activity : One milliliter of citrate buffer, pH 4.9, 1 ml of 0.01 M disodium phenylphosphate and 0.2 ml of serum were incubated for one hour, the reaction was stopped with 1 ml of 0.5 M NaOH followed by 1 ml of 0.5 M $NaHCO_3$, 1 ml of 4-aminoantipyrine (0.6%) and 1 ml of potassium ferricyanide (2.4%). Reddish brown colour was read at 510 nm wavelength. Phenol solution (as above) was used as standard.

ChE activity : A blank and test were prepared by placing 0.2 ml of serum with an equal volume of 0.15 M NaCl. The blank was placed in 60°C water bath for 10 minutes to inactivate the enzyme. Both test and blank were then treated with 2 ml of 5.38 mM m-nitrophenol in phosphate buffer, pH 7.8 and 0.2 ml of 0.83 M acetylcholine chloride. After incubation at 37°C for 30 minutes, the difference of absorbance between test and blank at 420 nm wavelength was used to derive ChE activity from calibration curve.

CPK activity : Serum (0.3 ml) was incubated with 1 ml of Tris-HCl buffer containing magnesium sulfate, pH 9.0, 1 ml of 60 mM creatine in the above buffer, and 0.1 ml of 0.5 mM ATP-glutathione at 37°C for 30 minutes. A blank was prepared by substituting buffer for the creatine solution. Following addition of 1.6 ml of 20% cold TCA, 1 ml of supernatant was mixed with 4 ml of water and treated with 1 ml of 1.25% molybdate solution and 0.25 ml of Fiske and SubbaRow reducer and again incubated for 30 minutes at room temperature. The absorbance for the test and blank was

read at 660 nm wavelength using water as reference. The Fiske and Subba-Row solution was prepared by dissolving 1g of Fiske and SubbaRow reducer (1-amino, 2-naphthol, 4-sulphonic acid; 0.8% sodium sulfite and sodium bisulfite) in 6.3 ml deionized water. The amount of inorganic phosphorus was determined from the calibration curve and then converted into activity.

ICDH activity : Serum (0.2 ml) was mixed with 0.4 ml of 10 mM DL-isocitrate trisodium, in 20 mM phosphate buffer, pH 7.8 followed by 0.2 ml of 10 mM manganese chloride in 0.15 M NaCl. Then 0.2 ml of NADP (3 mg/ml) was added in the test only and incubated at 37°C exac ly for 30 minutes. To stop the reaction 1 ml of 1.5 mM 2,4-dinitrophenyl hydrazine and then 0.5 ml of 5% EDTA was added, which was allowed to incubate for 30 minutes more. This was followed by addition of 4 ml of 0.5 N NaOH. After 5 minutes the absorbance was measured at 390 nm. The values were converted to activity from the calibration curve.

LDH activity : 0.1 ml of 6 fold diluted serum was incubated with 1 ml of 0.75 mM pyruvate in 150 mM phosphate buffer, pH 7.5 and NADH (1 mg/ml) for 30 minutes at 37°C followed by 1 ml of 1.5 mM 2,4-dinitrophenyl hydrazine. Mixture was allowed to stand at room temperature for 20 minutes before dilution with alkali (10ml of 0.4N NaOH). The absorbance of the test was measured at 525 nm against water and activity was derived from the standard curve.

SGOT activity : In 0.5 ml of 100 mM phosphate buffer, pH 7.5, 100 mM L-asparate and 2 mM 2-oxoglutarate, 0.2 ml of serum was incubated for 30 min. The reaction was stopped by 0.5 ml of 1.5 mM 2,4-dinitrophenyl hydrazine. The mixture was diluted with 0.4 N NaOH and after at least 5 minutes, the absorbance was read at 550 nm. The GOT activity was then derived from the calibration curve prepared for this purpose.

SGPT activity : In 0.5 ml of 100 mM phosphate buffer, pH 7.5, 100 mM DL-alanine, 2 mM 2-oxoglutarate was incubated with 0.1 ml serum for 30 minutes. The reaction was stopped by 0.5 ml of 1.5 mM 2,4-dinitrophenyl hydrazine and 0.4 N NaOH was used as a diluent. The absorbance was read after 5 minutes as mentioned in SGOT. The activity was then derived from standard curve.

In addition some other biochemical contents *i.e.* bilirubin according to Jendrassik and Grof (1938), cholesterol according to Liebermann and Burchard reaction as described in Henry and Henry (1974), free amino acids (FAA) according to Moore and Stein (1954), glucose according to Hartel *et al.* (1969), protein according to Lowry *et. al.* (1951) and urea according to DAM (diacetylmonoxime) method of Netelson *et al.* (1951) were also estimated. The absorbance of protein and FAA was converted from the standard curves prepared for this purpose.

Biochemical studies of liver

Aqueous liver extract (in ice cold saline) was used for the estimations of AP, GOT, GPT, ICDH, LDH activities and FAA, glucose and protein (soluble) contents. Cholesterol was estimated from ethanol-prepared extract. Total protein content was estimated from the tissue processed for nucleic acid estimation. For this purpose the pellet obtained after extraction of DNA and RNA was crushed with 2.5 ml of 0.5 N NaOH to solublize the protein fraction for estimation with Lowry's method (Lowry *et al.*, 1951).

Nucleic acid contents of liver were extracted by the method described in Shakoori and Ahmed (1973). Weighed amount of liver was crushed in boiling ethanol for 3 minutes. Three washings in ethanol were followed by 2-3 washings in methanol : ether (3 : 1) mixture. The curshed liver was then desiccated over dry NaOH under vacuum. RNA was extracted in 10% PCA at 4°C for 18 hours, while DNA was extracted in 10% PCA at 65°C for 30 minutes. DNA estimation was based on diphenylamine method and RNA estimation on orcinol method. Both these methods follow Schmidt and Thannhauser procedure described by Schneider (1957).

Histological studies

Histological sections of liver, after fixation in Bouin's fixative, were prepared according to the routine histological technique. The sections (8 μm thick) were cut after paraffin embedding and stained with hematoxylin and eosin. These sections were then studied to note various histopathological alterations. Morphometric studies on liver were also conducted and observations for the number of cells/microscopic field, number ofnuclei/cell, number of nucleoli/nucleus, size of hepatic cells, size of nuclei and size of nucleoli, were also taken,

The measurements were made with the help of an ocular micrometer which was calibrated with stage micrometer. The first three parameters were determined at magnification of 500X, while the rest of the studies were performed at a magnification of 1250X. The number of observations recorded for the first parameter were 9 that is 3 slides, one from each rat, were studied, by taking 3 fields from each slide. The number of observations for second to fourth parameter were 90 (i.e. from 3 slides, each from different animal, 3 fields of 10 cells/field were studied.

Statistical analysis

All the data were analysed statistically using one tailed student's t-test. Probability values (P) less than 0.05 were considered significant.

RESULTS

Effect of aldrin mixed diet (20 mg/kg body weight/day) administered for 48 hours

Body weight and liver weight

Aldrin feeding at above mentioned dose did not result in any adverse change in t e body weight of rats. The reducing trend (21 and 22%, respectively, at 24 and 48 hours) shown in Table I, was statistically non-significant. The RLW also showed non-significant increase (3.3%) in liver weight (Table I).

TABLE I : EFEECT OF ORAL FEEDING OF ALDRIN MIXED DIET (20 mg/kg BODY WEIGHT/DAY) FOR 48 HOURS ON THE BODY WEIGHT AND LIVER WEIGHT OF ALBINO RATS

Parameters	Control (n=8)	Aldrin feeding	
		24 hours (n=4)	48 hours (n=4)
Percent body weight gain/day	0.476±0.018[a]	0.376±0.048	0.372±0.045
Relative liver weight	2.750±0.090	2.732±0.054	2.845±0.016

[a]Mean±SEM.

Haematological studies

Aldrin administered at 20 mg/kg body weight/day for 48 hours produced typical reaction in the Hb content, RBC count and WBC count (Table II). The Hb content decreased 11 and 12%, respectively, after 24 and 48 hours of insecticide feeding. The RBC count was likewise decreased by 14%. The WBC count conversely increased 27 and 25%, respectively, after 24 and 48 hours. The PCV in control rats was 42.09±0.34%, which remained unaffected after aldrin treatment. The MCV and MCH was significantly increased, while the MCHC decreased 8-9% after insecticide treatment for 48 hours (Table II).

TABLE II : EFFECT OF FEEDING ALDRIN MIXED DIET (20mg/kg body weight/day) FOR A PERIOD OF 48 HOURS ON THE HAEMATOLOGICAL PARAMETERS OF ALBINO RATS.

Parameters[b]	Cotnrol (n=7)	Aldrin feeding	
		24 hours (n=4)	48 hours (n=4)
Hb (g/dl)	13.27±0.14[a]	11.77±0.19***	11.74±0.23***
RBC (X 10^6 cells/μl)	6.84±0.25	5.84±0.06**	5.89±0.12**
WBC (X 10^3 cells/μl)	6.36±0.26	8.11±0.13***	7.98±0.09***
PCV (%)	42.09±0.34	40.77±0.63	41.00±0.57
MCV (fl)	61.56±0.17	69.51±0.39***	69.70±0.46***
MCH (pg)	19.38±0.08	20.07±0.13**	19.95±0.15**
MCHC (g/dl)	31.52±0.09	28.88±0.24***	28.61±0.23***

[a]Mean ± SEM, Student's 't' test ; *P < 0.05; **P < 0.01; ***P < 0.001.

[b]Abbreviations used : dl, decilitre=100 ml; fl, femtolitre $=10^{-15}$ litre; Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration ; MCV, mean corpuscular volume; PCV, packed cell volume; pg, picogram= 10^{-12}g; TEC, total erythrocytic count ; TLC, total leukocytic count.

Biochemical analysis of blood

Table III shows the effect of aldrin feeding for 48 hours on the various enzymatic activities of rat blood serum. Almost all the enzyme activities except for GPT, were significantly raised. The effect on AP activity was more severe as compared with AcP. After 24 and 48 hours of aldrin administration,

the increase in AP activity was 51 and 141 %, while the increase in AcP activity was 26 and 15 %, respectively. The GOT activity was the most drastically affected. The activity increased 100% and 369 % after 24 and 48 hours of insecticide feeding. The LDH and ICDH activities also showed increase after insecticide treatment. The LDH activity showed 46 and 78% and ICDH activity showed 61 and 135 % increase after 24 and 48 hours respectively. The CPK activity was affected only after 48 hours of insecticide exposure, when it inreased 31 % and was not significantly affected after 24 hours of aldrin administration. Amylase, just like CPK, showed an increase of 60 % over the control activity at 48 hour treatment. The ChE activity increased 58 and 88 % during the same periods, respectively (Table III).

TABLE III : EFFECT OF FEEDING ALDRIN MIXED DIET (20 mg/kg body weight/day) FOR 48 HOURS ON SOME BIOCHEMICAL COMPONENTS OF ALBINO RAT BLOOD SERUM

Parameters[b]	Control (n=8)	Aldrin feeding	
		24 hours (n=4)	48 hours (n=4)
Ap (KAU/dl)	11.67± 0.16[a]	17.62± 0.72***	28.11± 1.12***
AcP (KAU/dl)	4.23± 0.20	5.31± 0.34*	4.85± 0.16*
Amylase (SoU/dl)	216.77± 8.02	238.82±10.76	327.27±16.82***
ChE (RU/ml)	24.37± 1.42	38.40± 4.34*	45.75± 4.77**
CPK (SiU/ml)	9.01± 0.63	10.70± 0.64	11.82± 0.32**
ICDH (SiU/ml)	243.18±14.80	392.48±23.05***	570.26±44.04***
LDH (IU/l)	465.66±26.29	678.12±21.10***	827.64±25.55***
SGOT (IU/l)	21.73± 1.65	43.49± 2.40***	101.99± 5.31***
SGPT (IU/l)	23.05± 2.40	23.16± 1.81	23.67± 2.21
Bilirubin (mg/dl)	0.72± 0.07	0.47± 0·03**	0.51± 0.07
Cholesterol (mg/dl)	195.64± 6·94	135.34± 6.78***	139.06± 5.33***
Free amino acids (mg/dl)	7.26± 0.19	6.21± 0.05***	5.93± 0.28**
Glucose (mg/dl)	107.37± 3.36	119.99± 5.94	137.74± 4.76***
Protein (g/dl)	7.30± 0.13	8·28± 0.23**	9.18± 0.40**
Urea (mg/dl)	35.49± 0.96	33.63± 1.03	24.46± 1.54***

[a]Mean ± SEM, Student's 't' test ; *P<0.05; **P<0.01; ***P<0.001.

[b]Abbreviations used : AP, alkaline phosphatase ; AcP, acid phosphatase; ChE, cholinesterase ; CPK, creatinephospho kinase ; ICDH, isocitrate dehydrogenase; LDH, lactate dehydrogenase ; SGOT, serum glutamate oxaloacetate transaminase ; SGPT, serum glutamate pyruvate transaminase.

Definition of enzyme units : KA (King Armstrong) U (AP), liberation of 1 mg of phenol in 15 minutes under the conditions of the test ; KAU (AcP), liberation of 1 mg of phenol in 60 minutes under fest conditions ; SoU (Somogyi units), amount of enzyme digested 5mg of starch in 15 minutes under test conditions ; RU (Rappaport units), amount of enzyme that will liberate one micromle of acetic acid from acetylcholine in 30 minutes under the test conditions; SiU (Sigma units, for CPK), amount of enzyme that will phosphorylate one nanomole of creatine per minute at 25 °C under the conditions of the test; SiU (for ICDH), quantity of enzyme that will produce one nanomole of NADPH in one hour under conditions of the test ; IU (international unit), transformation of one micromole substrate in one minute under the conditions of the test.

The serum proteins increased after aldrin treatment, while the FAA decreased during the same period (Table III). The serum proteins increased 13 and 26%, while the FAA content decreased 14 and 18% after 24 and 48 hours of aldrin treatment. The bilirubin, cholesterol and urea contents decreased during the same period after insecticide treatment. The bilirubin decreased 35 and 29% from control level of 0.72±0.07 mg/100 ml, while the cholesterol content decreased 31 and 29% after 24 and 48 hours of aldrin treatment, respectively. The urea content, initially remained unaffected and showed 31% decrease after 48 hours of aldrin treatment. The glucose content likewise decreased 12 and 28% after 24 and 48 hours of aldrin administration (Table III).

Biochemical analysis of liver

The hepatic enzymes were not affected to that extent, as they were in the blood serum after aldrin treatment. In fact GPT and ICDH activities were not affected at all, while the LDH and GOT activities were significantly altered only after 48 hours of aldrin feeding (Table IV). The control liver showed 7.11±0.38 IU/g GOT activity, which increased 18 and 28%, 24 and 48 hours after aldrin administration. The LDH activity, on the other hand, decreased 26% after 48 hours of aldrin treatment. The hepatic AP activity was, however, drastically affected, which increased 69% and 171% after 24 and 48 hours of aldrin feeding.

Table IV shows the effect of aldrin feeding on the various biochemical components of liver other than enzymes. The nucleic acids (both DNA and RNA) did not show any significant change after aldrin treatment, while the total proteins showed 19 and 13% increase during the same period *i.e.* 24 and 48 hours after aldrin treatment. The soluble proteins likewise, showed increase of 13 and 18%, but conversely, FAA content decreased 32 and 37% after 24 and 48 hours, respectively. The cholesterol content in control rat liver was 7.62±0.22 mg/g while the glucose content was 20.14±0.53 mg/g. The cholesterol contents decreased 29% (24 hours treatment) while the glucose contents decreased 43% (48 hours treatment) after aldrin treatment (Table IV).

TABLE IV : EFFECT OF FEEDING ALDRIN MIXED DIET (20 mg/kg body weight/ day) FOR A PERIOD OF 48 HOURS ON HEPATIC BIOCHEMICAL COMPONENTS OF ALBINO RATS.

Parameters	Control	Aldrin feeding	
		24 hours	48 hours
	(n=5)	(n=4)	(n=4)
AP (KAU/g)	0.80±0.16[a]	1.36±0.17*	2.18±0.09***
GOT (IU/g)	7.11±0.38	8.40±0.51	9.11±0.56*
GPT (IU/g)	7.32±0.68	7.88±0.55	10.21±1.22
ICDH (XIO^3 SiU/g)	31.39±0.78	27.71±3.16	31.20±2.46
LDH (XIO^4 IU/g)	56.57±4.43	66.24±3.32	41.83±2.76
Cholesterol (mg/g)	7.62±0.22	5.35±0.50**	5.42±1.06
Free amino acid (µg/g)	399.21±18.13	273.24±10.51***	250.23±20.27***
Glucose (mg/g)	20.14±0.53	20.44±0.76	11.57±0.29***
Soluble protein (mg/g)	111.18±5.08	125.41±10.25	142.17±12.01*
Total protein (mg/g)	199.33±6.11	237.38±8.21**	174.02±10.58
DNA (mg/g)	3.84±0.44	2.99±0.33	2.54±0.45
RNA (mg/g)	9.53±0.55	10.44±1.72	9.04±0.75

[a]Mean ± SEM, Student's 't' test ; *P < 0.05 ; **P < 0.01 ; ***P < 0.001
For other details, see Table III.

Histological structure of liver

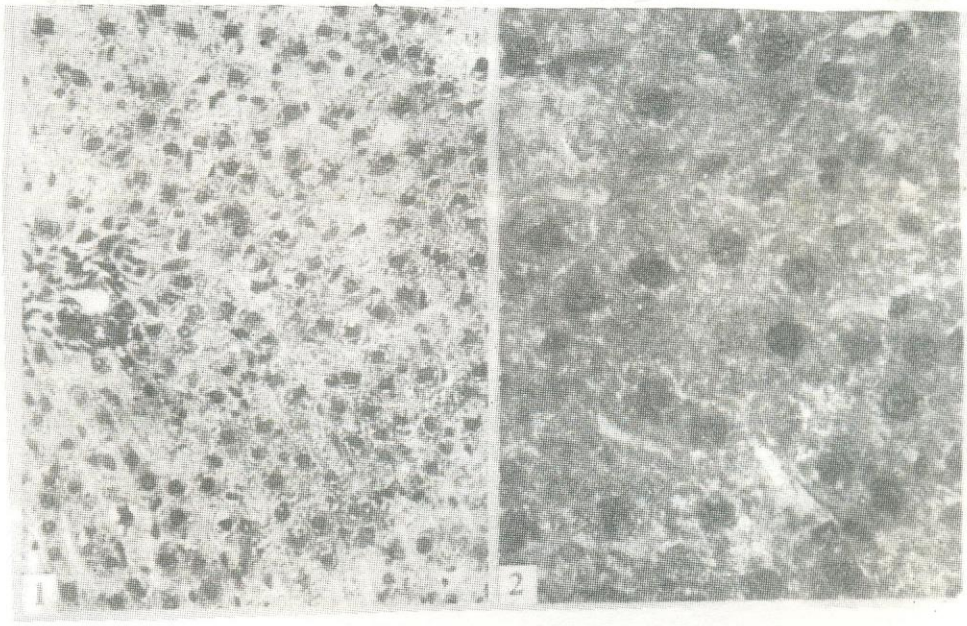
Table V shows the effect of aldrin feeding on various histological parameters of male albino rat livers. The size of hepatic cell, its nucleus and nucleolus increased tremendously after insecticide treatment for a total period of 48 hours. The hepatic cell size increased 33 and 41%, respectively after aldrin treatment for 24 and 48 hours. The nuclear size increased 44 and 31%, while the nucleolus showed 88 and 79% increase during the same period. The number of nuclei/cell and number of nucleoli/nucleus remained

unaltered, while the number of cells/field exhibit significant decrease which is indicative of cellular hypertrophy (Table V).

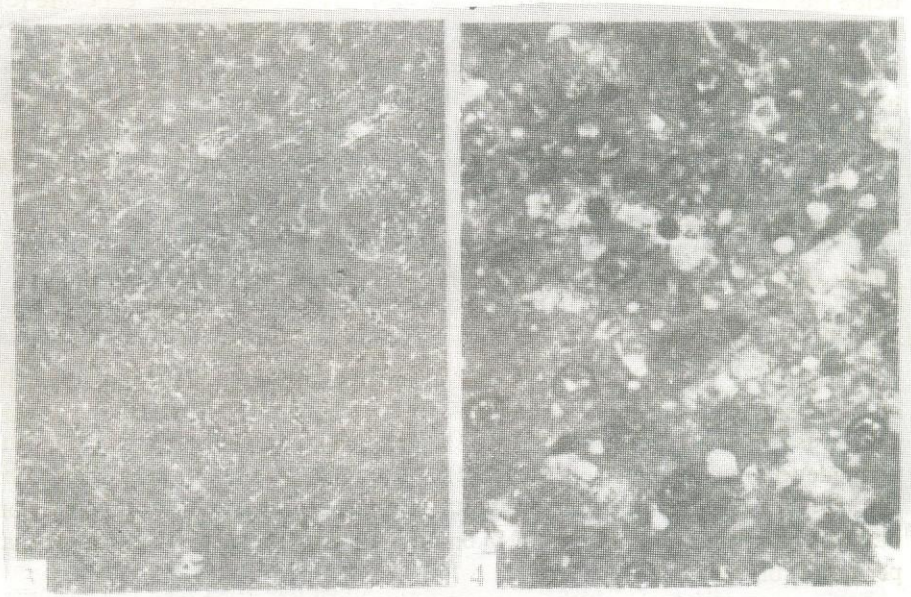
TABLE V : EFFECT OF FEEDING ALDRIN MIXED DIET (20 mg/kg body weight/day) FOR 48 HOURS ON THE VARIOUS HISTOLOGICAL PARAMETERS OF RAT LIVER

Parameters	Control	Aldrin feeding	
		24 hours	48 hours
No. of cells/ field (n=9)	252.91±8.54[a]	230.41±6.24	212.68±11.64*
No. of nuclei/ cell (n=90)	1.13±0.19	1.16±0.04	1.13±0.04
No. of nucleoli/ nucleus (n=90)	1.47±0.11	1.52±0.08	1.53±0.09
Size of cell (μ^2 ; n=90)	279.79±14.24	373.26±12.68**	391.92±1.84***
Size of nucleus (μ^2 ; n=90)	47.29±2.01	68.01±1.93***	62.05±1.83***
Size of nucleolus (μ^2 ; n=90)	2.94±0.26	5.52±0.35***	5.26±0.32***

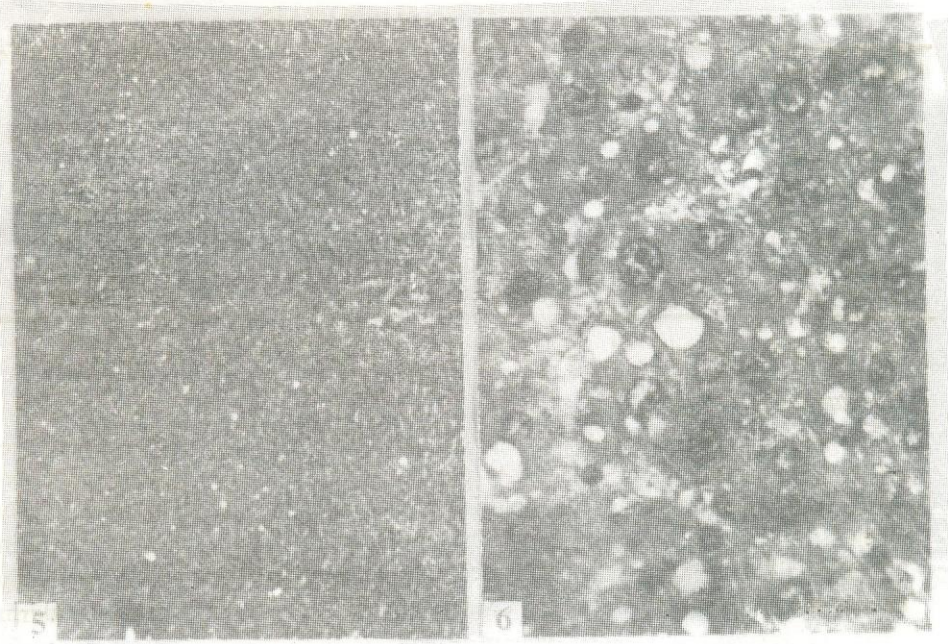
[a]Mean±SEM, Student's 't' test ; *P> 0.05 ; **P < 0.01 ; ***P < 0.001.



Figs.1-2
Histological structure of normal rat liver, Note the portion of a hepatic lobule, linear cords (1) and arrangement of cells and nuclei (2). Magnifications: 1, 100X; 2, 250X. Stain: Hematoxylin and Eosin (H & E).



Figs.3-4
Histological structure of rat liver fed on aldrin-mixed diet for 24 hours. Note the disturbed lobular structure, necrotic area (3) vacuolation, fatty degeneration and hypertrophied cells (4). Magnifications: 3; 50X; 4. 250X. Stain: H & E.



Figs.5-6.
Histological structure of rat liver fed on aldrin-mixed diet for 48 hours. Note the alterations in general lobular structure (5) hypertrophied cells and nuclei; Vacuolation and fatty degeneration (6). Magnifications: 5, 50X; 6. 250X. Stain: H & E.

The hepatic cells, their nuclear and nucleolar hypertrophy after insecticide treatment was obvious from Figs. 3-6. The insecticide exposure for 48 hours had much more prominent and drastic effect as compared to 24 hours treatment. Comparison of Fig. 2 (control) with Fig. 4 (24 hours) and Fig. 6 (48 hours) highlights the effect of insecticide. Nuclei were prominently vesicular with well defined nucleoli. The entire hepatic lobule was marked by extensive vacuolation, which was a typical sign of toxicity. In certain cases a part of the liver tissue was seen to develop fatty degeneration and signs of necrosis (Figs. 4-6).

Effect of aldrin mixed diet (8 mg/kg body weight/day) administered for 15 days

Body weight and liver weight

The body weight gain in rats decreased after administration of aldrin at this dose. After a slight non-significant change at 3 and 6 days, this gain was reduced significantly by 40, 44 and 43% at 9, 12 and 15 days of insecticide feeding, respectively (Table VI). The RLW, which showed sharp rise till day 6 of insecticide feeding, indicated signs of recovery (38% increase on day 6 as compared with 14 and 19% on day 12 and 15, respectively) after that period (Table VI).

TABLE VI : EFFECT OF FEEDING ALDRIN MIXED DIET (8 mg/kg body weight/day) FOR A PERIOD OF 15 DAYS ON THE BODY WEIGHT AND LIVER WEIGHT OF ALBINO RATS.

Aldrin feeding	Percent body weight gain/day	Relative liver weight
Control (n=7)	0.520±0.039[a]	2.76±0.05
3 Day (n=4)	0.556±0.047	3.76±0.18***
6 Day (n=4)	0.509±0.041	3.82±0.14**
9 Day (n=4)	0.300±0.025**	3.49±0.11***
12 Day (n=4)	0.292±0.023***	3.15±0.12*
15 Day (n=4)	0.290±0.012***	3.29±0.02***

[a]Mean ± SEM, Student's 't' test ; *P<0.05 ; **P < 0.01 ; ***P < 0.001.

Haematological studies

Aldrin administered for 15 days caused significant decrease in the Hb content, RBC count and PCV (Table VII). The Hb content decreased significantly from 6 days of aldrin treatment till day 15, continuously when it showed 12% decrease. The RBC count was affected within 3 days of aldrin feeding, when 10% decrease was noticed. This count gradually decreased (22%) till day 15. The PCV was affected only after 9 days of aldrin

feeding and continued to decrease till day 15 (Table VII). The WBC on the other hand, was conversely affected which increased 20% within three days of aldrin treatment. This increase was regular till day 15, and reached upto 45%. The various other haematological parameters such as MCV and MCH were also significantly increased after aldrin treatment for 15 days. The MCHC, on the other hand, decreased during this treatment. The decrease was generally 6-7% (Table VII), which was quite significant.

TABLE VII : EFFECT OF FEEDING ALDRIN MIXED DIET (8 mg/kg body weight/day) FOR 15 DAYS ON THE VARIOUS HAEMATOLOGICAL PARAMETERS OF ALBINO RATS.

Parameters	Control	Aldrin feeding				
	n=6	3 days (n=4)	6 days (n=4)	9 days (n=4)	12 days (n=4)	15 days (n=4)
Hb (g/dl)	13.04[a] ±0.16	12.71 ±0.19	12.08** ±0.19	11.78*** ±0.18	11.63** ±0.33	11.48*** ±0.19
RBC (X10⁶ cells/μl)	6.91 ±0.12	6.24** ±0.09	6.02** ±0.16	5.82*** ±0.14	5.54*** ±0.11	5.37*** ±1.90
WBC (X10³ cells/ μl)	6.55 ±0.52	7.80 ±0.23	8.85** ±0.32	8.72** ±0.38	9.60** ±0.49	9.49** ±0.44
PCV (%)	43.28 ±0.40	42.84 ±0.35	42.97 ±0.25	41.93* ±0.33	40.97*** ±0.43	40.61** ±0.44
MCV (fl)	62.64 ±0.46	68.70*** ±0.47	71.49*** ±1.47	72.07*** ±1.15	72.51*** ±0.83	75.70*** 2.94
MCH (pg)	18.88 ±0.28	20.29** ±0.04	20.06* ±0.22	20.23** ±0.18	20.97** ±0.31	21.39*** ±0.34
MCHC (g/dl)	30.15 ±0.36	29.54 ±0.23	28.06* ±0.29	28.09** ±0.22	28.94 ±0.58	28.27** ±0.23

[a]Mean±SEM, Student's 't' test ; *P<0.05 ; **P<0.01 ; ***P<00.01.
For other details, see Table II.

Biochemical analysis of blood

Table VIII showed the effect of aldrin administered for 15 days on the various enzymatic activities of rat blood serum.

Activities of most of the enzymes such as AcP, AP , amylase, SGOT, SGPT, LDH and CPK increased after aldrin feeding. Usually the increase in activity was accelerated with increasing duration of insecticide administration. Most of these enzymes were drastically affected within three days of aldrin feeding. The AP activity increased94, 129, 240, 278 and 368%

after 3, 6, 9, 12 and 15 days of insecticide feeding. The AcP activity likewise, increased 115, 194, 256, 142 and 105%, respectively, during the same period. The SGOT activity showed an increase of 136, 143 and 195 % after 9, 12 and 15 days of feeding. The increase in SGPT activity was 88, 117, 73, 75 and 23% on day 3, 6, 9, 12 and 15 (Table VIII). From amongst dehydrogenases, LDH activity was increased by 39, 49, 96, 103 and 115%, while ICDH activity decreased by 41, 40, 11, 23 and 22% during the same observation periods. The CPK activity also increased significantly (83%) after 9 days of aldrin

TABLE VIII : EFFECT OF FEEDING ALDRIN MIXED DIET (8 mg/kg body weight/day) FOR 15 DAYS ON VARIOUS BIOCHEMICAL COMPONENTS OF RAT BLOOD SERUM.

Parameters	Control	Aldrin feeding				
	(n=7)	3 days (n=4)	6 days (n=4)	9 days (n=4)	12 days (n=4)	15 days (n=4)
AcP (KAU/dl)	3.63[a] ±0.26	7.82*** ±0.38	10.68*** ±0.71	12.92*** ±1 08	8.77*** ±0.49	7.45*** ±0.28
AP (KAU/dl)	8.57 ±0.39	16.64** ±2.14	19.58*** ±1.60	29.15*** ±1.32	32.36*** ±2.59	40.09*** ±2.78
Amylase (SoU/dl)	226.76 ±14.45	309.23** ±18.86	384.61*** ±18.11	354.28* ±39.03	429.62*** ±21.80	473.91*** ±41.47
ChE (RU/ml)	34.77 ±2.34	24.00* ±3.06	28.72 ±2.56	29.62 ±3.74	29.25 ±4.17	32.21 ±4.59
CPK (SiU/ml)	9.66 ±0.60	9.12 ±0.55	13.81 ±2.37	17.67*** ±1.10	14.76** ±1.15	18.87*** ±1.11
ICDH (SiU/ml)	428.76 ±12.93	254.36*** ±9.25	256.18*** ±18.18	380.18* ±15.48	328.66*** ±15.76	335.96* ±34.69
LDH (IU/l)	506.56 ±21.91	702.48*** ±17.53	754.32*** ±25.85	990.96*** ±50.55	1029.24*** ±38.51	1090.20*** ±56.24
SGOT (IU/l)	27.80 ±1.48	28.74 ±1.65	34.12 ±3.83	65.74*** ±2.87	67.49*** ±2.63	81.99*** ±2.87
SGPT (IU/l)	22.39 ±1.60	41.99*** ±3.16	48.59*** ±1.87	38.66** ±4.06	39.11** ±2.91	27.47 ±3.89
Bilirubin (mg/dl)	0.76 ±0.04	1.87*** ±0.11	1.67** ±0.24	1.34*** ±0.11	1.29** ±0.12	1.24*** ±0.07
Cholesterol (mg/dl)	180.73 ±7.16	172.38 ±7.37	170.48 ±9.17	161.32 ±7.31	158.07 ±15.84	159.44 ±15.30
Free amino acids (mg/dl)	9.81 ±0.14	7.68** ±0.53	6.31*** ±0.39	6.44*** ±0.51	6.35*** ±0.42	4.36*** ±0.17
Glucose (mg/dl)	129.60 ±7.08	94.61* ±8.85	88.37** ±5.43	68.87*** ±5.61	90.15 ±5.07	96.08* ±8.79
Protein (g/dl)	8.04 ±0.21	7.64 ±0.16	8.56 ±0.28	9.78* ±0.52	9.71** ±0.36	10.54*** ±0.44
Urea (mg/dl)	33.56 ±1.19	42.99*** ±2.36	42.50** ±1.16	51.44** ±3.31	67.76*** ±2.13	57.00*** ±2.95

[a]Mean±SEM, Student's 't' test ; *P < 0.05 ; **P < 0.01 ; ***P < 0.001.
For other details, see Table - III.

feeding. The maximum rise (95%) was after 15 days of intoxication. The amylase activity likewise, increased within three days of insecticide feeding. The increase was 36, 70, 56, 90 and 109% after 3, 6, 9, 12 and 15 days of insecticide feeding, respectively. Cholinesterase was the only enzyme activity, which was least affected by aldrin feeding. Except for first 3 day observation, when its activity was decreased by 31%, all other deviations were non-significant (Table VIII).

Table VIII also shows the effect of aldrin feeding on the various biochemical components of blood serum other than enzymes. The bilirubin, which is a breakdown product of haemoglobin, increased 147, 121, 77, 71 and 64% after 3, 6, 9, 12 and 15 days of insecticide treatment which also indicated gradual recovery as the feeding was prolonged. The urea content likewise increased 28, 27, 53, 102 and 70% during the same observation period. The total serum protein content also increased, but this rise was significant after 9 days of aldrin feeding, when it was 22% more than the control and showed maximum rise of 31% at 15 day treatment. The FAA content was highly sensitive and decreased 22, 36, 34, 35 and 56% after 3, 6, 9, 12 and 15 days of aldrin treatment ($P<0.001$; $n=4$). The glucose content also decreased prominently during the initial period but showed slight recovery after 12 days (Table VIII). The cholesterol content, however, remained unaltered.

Biochemical analysis of liver

Most of the hepatic enzymatic activities and other biochemical components were significantly affected after oral administration of aldrin at a dose of 8 mg/kg body weight/day for 15 days (Table IX).

From amongst hepatic enzymes, the AP and ICDH activities increased within three days of insecticide feeding. The hepatic AP activity showed an increase of 80, 73, 133, 144 and 172%, while the ICDH activity showed an increase of 121, 56, 132, 142, and 100% after 3, 6, 9, 12 and 15 days of aldrin feeding in both cases. The LDH activity was affected only at 9 and 12 days of aldrin feeding, when the activity was 23% and 18% more than the control, respectively. The GOT activity was likewise affected after 9 days of feeding ($P<0.01$) and showed 186, 158 and 171% increase after 9, 12 and 15 days of insecticide feeding. The GPT activity, however, generally remained unaffected except for 3 days feeding observation, when this activity showed about 37% increase over the control value (Table IX).

TABLE IX : EFFECT OF FEEDING ALDRIN MIXED DIET (8mg/kg body weight/day) FOR 15 DAYS ON SOME BIOCHEMICAL COMPONENTS OF RAT LIVER.

Parameters	Control	Aldrin feeding				
		3 days	6 days	9 days	12 days	15 days
	(n=7)	(n=4)	(n=4)	(n=4)	(n=4)	(n=4)
AP (KAU/g)	0.64[a] ±0.02	1.15*** ±0.05	1.11*** ±0.08	1.49*** ±0.16	1.56** ±0.17	1.74*** ±0.06
GOT (IU/g)	7.34 ±0.17	8.34 ±0.78	14.46 ±3.24	20.96** ±2.96	18.92*** ±0.82	19.88** ±2.80
GPT (IU/g)	11.07 ±0.25	6.98** ±0.94	11.59 ±2.01	13.60 ±2.33	11.85 ±1.38	12.90 ±3.09
ICDH ($X10^3$ SiU/g)	20.10 ±0.50	44.33** ±3.17	31.36** ±3.13	46.60** ±4.96	48.55*** ±3.51	40.23** ±4.00
LDH ($X10^4$ IU/g)	51.90 ±1.20	47.21 ±2.77	53.72 ±3.24	63.76** ±3.06	61.12** ±1.68	57.67 ±4.07
Cholesterol (mg/g)	15.72 ±50.35	5.32*** ±0.51	8.09** ±1.40	5.44*** ±0.44	5.63*** ±0.48	4.41*** ±0.37
Glucose (mg/g)	12.93 ±0.61	19.65*** ±1.03	22.99*** ±0.32	23.24*** ±0.41	25.60 ±3.43	31.41*** ±1.43
Free amino acids (µg/g)	319.95 ±12.68	312.86 ±11.61	312.36 ±13.66	489.37*** ±20.75	410.71** ±13.08	503.18*** ±13.35
Soluble proteins (mg/g)	152.99 ±5.62	127.52 ±14.95	151.33 ±4.85	156.69 ±3.09	170.62 ±5.80	174.51 ±8.40
Total proteins (mg/g)	233.67 ±7.45	190.40* ±11.36	253.85 ±5.74	278.82** ±7.66	297.88 ±12.75	311.27*** ±11.66
DNA (mg/g)	2.42 ±0.17	1.99 ±0.16	2.52 ±0.14	2.47 ±0.14	2.53 ±0.06	2.65 ±0.21
RNA (mg/g)	8.62 ±0.38	12.93** ±0.75	14.41*** ±0.60	16.52*** ±1.32	22.24*** ±2.40	18.42* ±3.31

[a]Mean ± SEM, Student's 't' test ; *P < 0.05 ; **P < 0.01 ; ***P < 0.001

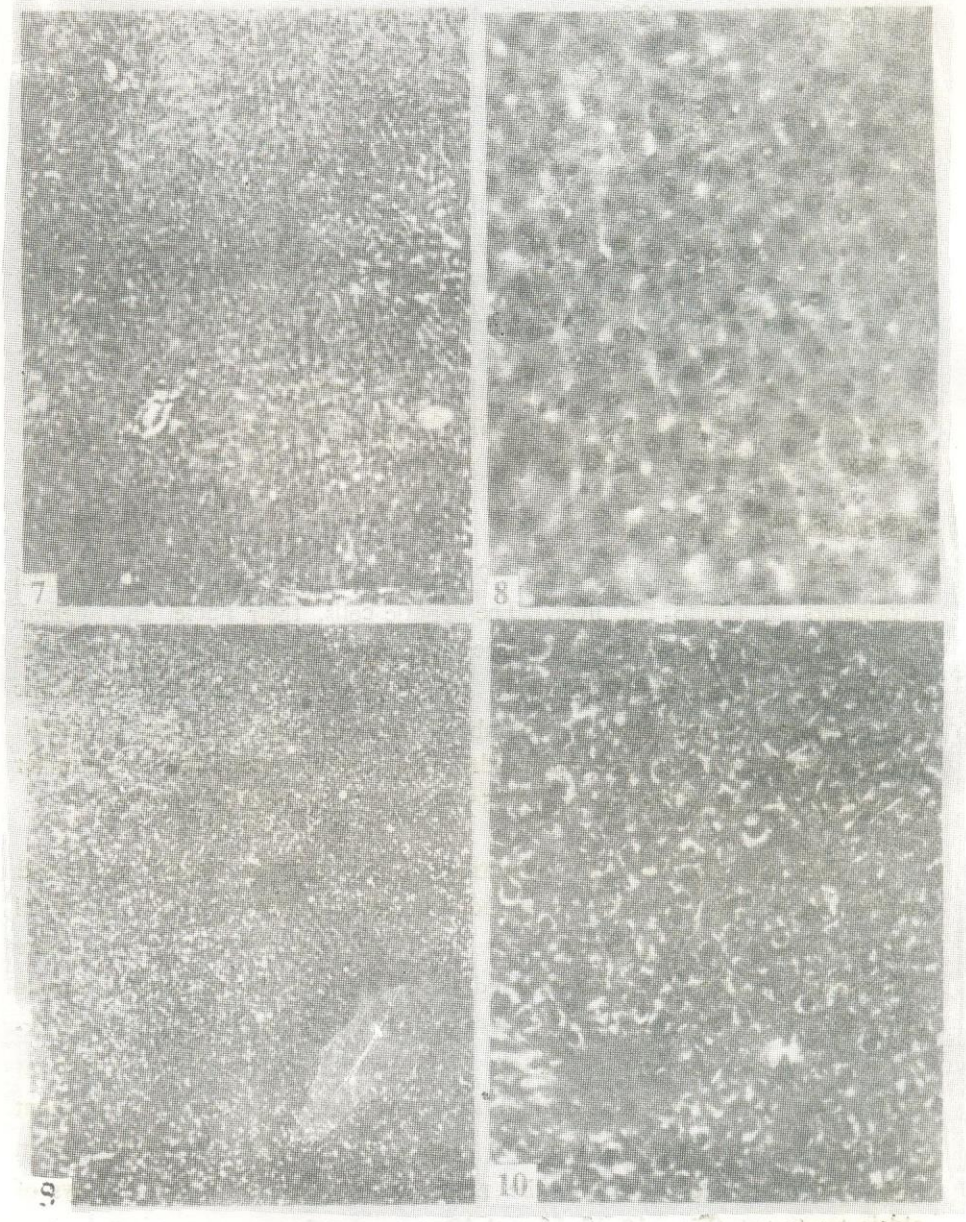
For other details, see Table - III.

Table IX also shows the effect of aldrin feeding on various biochemical components of liver other than enzymes. The hepatic cholesterol content decreased significantly. This decrease 3, 6, 12 and 15 days after insecticide feeding was 66, 49, 65, 64 and 72%, respectively ($P<0.001$). The glucose content, on the other hand, increased after aldrin feeding. The increase was 52, 78, 80, 98 and 143% after same durations of insecticide feeding, which indicates gradual induction of hyperglycemic conditions in liver of rats. The soluble proteins did not show any significant change after insecticide treatment. The total proteins, on the other hand, after initial decrease (19%) during the first three days gradually increase to 9, 19, 28 and 33% on day 6, 9, 12 and 15 of insecticide feeding. These changes were statistically significant except 6 day feeding observation. The hepatic FAA did not show any change until day 9, when value increased by 53% and rise was maximum (57%) at 15 day treatment. Amongst the nucleic acids the DNA content remained unaltered, while the RNA content increased 50, 67, 92, 158 and 114% after 3, 6, 9, 12 and 15 days of aldrin feeding (Table IX).

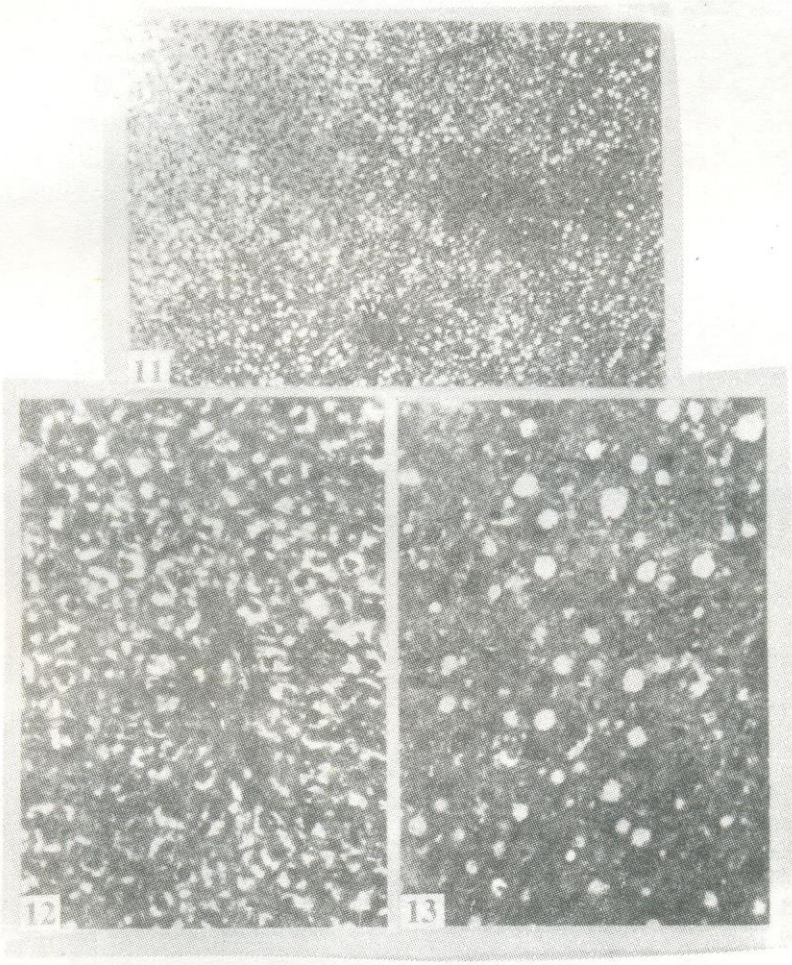
Histological structure of liver

Table X shows the effect of aldrin on the various histological parameters of albino rat liver. The hepatic cells, their nuclei and nucleoli were significantly hypertrophied. The degree of hypertrophy increased with the duration of insecticidal treatment. The number of hepatic cells/microscopic field decreased accordingly. The number of nuclei/cell and number of nucleoli/nucleus remained unchanged under aldrin intoxication except for the number of nucleoli/nucleus which increased 25% after 15 days of aldrin feeding.

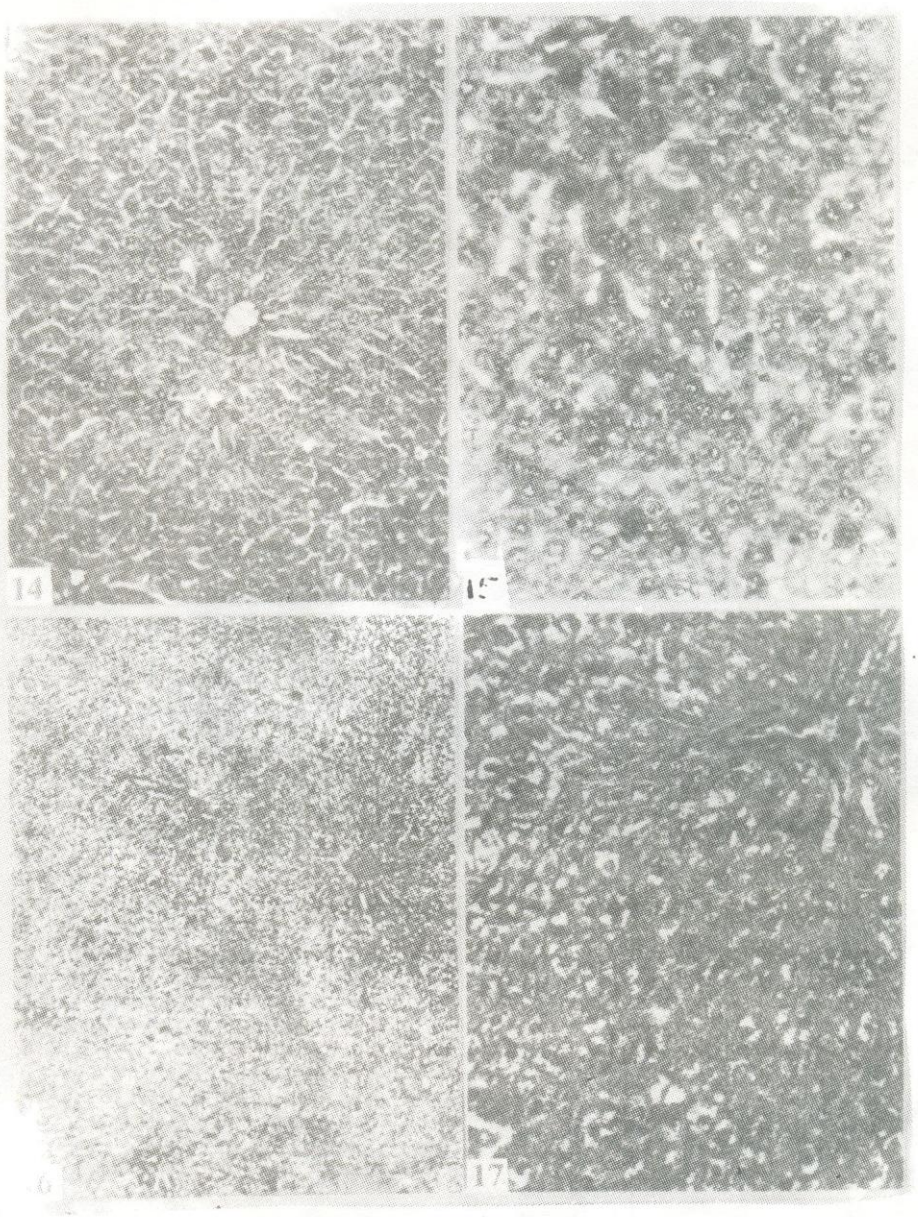
That the hepatic cells hypertrophy, and that the hepatic nuclei and nucleoli were also enlarged is abundantly clear from Figs. 7-15. The nuclei were vesicular during the first three days of feeding (Fig. 8), but were converted into irregular shaped condensed bodies during prolonged feeding (Figs. 12, 13 and 17). The hepatic structure after 9 days aldrin feeding was marked by extensive vacuolation (Figs. 11-13). Most of the hepatic cells at higher doses have extensive granulation in cytoplasm (Figs. 15, 17). Prominent cytoplasmolysis appeared in the cells around nuclei which is evident from large and clear areas arround the nuclei in the case of 6, 9 and 15 days of aldrin treatment (Figs. 10, 12, 16 and 17).



Figs.7-10
Histological structure of rat liver fed on aldrin-mixed diet for 3 days (7-8) and 6 days (9-10). Note the changes in normal lobular pattern (7,9) increase in kupffer cells and irregular clear areas (8), nerotic zones, atrophty of hepatic tissue and clear areas arround nuclei (9-10). Magnifications: 7,9, 25X; 8,10, 100X, Stain: H & E



Figs.11-13.
Histological structure of rat liver fed on aldrin-mixed diet for 9 days. Note the change in general lobular morphology, numerous rounded clear areas (vacuolation) in the tissues (11, 13), margination and irregular shaped nuclei (12). Magnifications: 11, 25X; 12, 100X. Stain: H & E.



Figs.14-17
Histological structure of rat liver fed on aldrin-mixed diet for 12 days (14-15) and 15 days (16-17). Note the change in lobular morphology (14), number of elongated (rod shape) clear areas in the tissues, hypertrophied cells (15), extensive cytoplasmic margination, vacuolations and irregular clear nuclei (16,17). Magnifications 14, 50X; 15, 17, 100X; 16, 25X. Stain: H&E.

TABLE X : EFFECT OF FEEDING ALDRIN MIXED DIET (8 mg/kg body weight/day) FOR 15 DAYS ON THE VARIOUS HISTOLOGICAL PARAMETERS OF ALBINO RAT LIVER.

Parameters	control	Aldrin feeding				
		3 days	6 days	9 days	12 days	15 days
No. of cells/ field (n=9)	257.54±9.78[a]	240.50±8.09	235.97±5.37	228.72±11.24	214.32±10.47*	223.48±9.57*
No. of nuclei/ cell (n=90)	1.09±0.03	1.14±0.04	1.10±0.05	1.16±0.04	1.11±0.33	1.17±0.04
No. of nucleoli/ nucleus (n=90)	1.63±0.10	1.92±0.14	1.73±0.05	1.83±0.08	1.74±0.10	2.03±0.13*
Size of cell (μ^2 ; n=90)	281.03±9.62	369.75±7.41***	389.42±9.74***	407.48±17.25***	432.00±15.42***	428.33±0.36***
Size of nucleus (μ^2 ; n=90)	42.51±1.79	59.13±1.72***	61.32±1.55***	63.62±1.80***	70.30±2.09***	68.48±2.04***
Size of nucleolus (μ^2 ; n=90)	3.09±0.22	4.70±0.34**	4.35±0.29*	4.67±0.24	4.68±0.31**	5.68±0.36***

[a]Mean ± SEM, Student's 't' test ; *P < 0.05 ; **P < 0.01 ; ***P < 0.001

Effect of aldrin mixed diet (2.5 mg/kg body weight/day) administered for a period of 6-18 months

Body weight and liver weight

The total body weight gain of rats was significantly reduced after feeding insecticide mixed diet at above mentioned dose for 18 month period. Table XI revealed 22.5, 34 and 33.6% reduction in body weight gain after continuous administration of aldrin for 6, 12 and 18 months. The rat liver also showed signs of enlargement which was evident from the increase in RLW of the animals. Initially at 6 month feeding period the liver : body weight ratio remained unaffected, but after that 7.5 and 11.4% rise in RLW was observed at 12 and 18 months of aldrin treatment, respectively (Table XI).

TABLE XI : EFFECT OF FEEDING ALDRIN MIXED DIET (2.5 mg/kg body weight/day) FOR A PERIOD OF 6-18 MONTHS ON THE BODY AND LIVER WEIGHT OF ALBINO RAT.

Parameters	6 months aldrin feeding experiment		12 months aldrin feeding experiment		18 months aldrin feeding experiment	
	Control (n=6)	Aldrin fed (n=3)	Control (n=4)	Aldrin fed (n=3)	Control (n=6)	Aldrin fed (n=3)
Percent body weight gain/day	0.675[a] ±0.053	0.523 ±0.220	0.593 ±0.050	0.390 ±0.017	0.512 ±0.021	0.340 ±0.026
Relative liver weight	2.55 ±0.05	2.59 ±0.01	2.64 ±0.07	2.84* ±0.03	2.37 ±0.08	2.64* ±0.07

[a]Mean±SEM, Student's 't' test; *P<0.05.

Haematological studies

Table XII shows the effect of long term feeding of aldrin on the various haematological parameters of male albino rats. The Hb content, RBC count and PCV decreased after long term feeding. The Hb content decreased by 29-30%, the RBC count by 15-18%, while PCV by 5-9%. The WBC count, as in other typical insecticide exposure cases, increased by 5-11%. Table XII shows a distinct increase in MCV and MCH in all treatments, while decrease in MCHC was non-significant after aldrin treatment.

TABLE XII : EFFECT OF FEEDING ALDRIN MIXED DIET (2.5 mg/kg body weight/day) FOR A PERIOD OF 6-18 MONTHS ON THE VARIOUS HAEMATOLOGICAL PARAMETERS OF ALBINO RATS.

Para meters	6 months aldrin feeding experiment		12 months aldrin feeding experiment		18 months aldrin feeding experiment	
	Control (n=6)	Aldrin fed (n=4)	Control (n=4)	Aldrin fed (n=3)	Control (n=6)	Aldrin fed (n=4)
Hb (g/dl)	13.79[a] ±0.32	11.88** ±0.29	13.14 ±0.23	11.90* ±0.21	13.04 ±0.16	11.70** ±0.22
RBC (X10^6 cells/μl)	7.09 ±0.13	5.78*** ±0.10	7.05 ±0.13	5.94*** ±0.10	6.91 ±0.12	5.89*** ±0.16
WBC (X10^3 cells/μl)	6.65 ±0.40	6.99 ±0.11	6.24 ±0.13	6.92* ±0.18	6.55 ±0.52	7.02 ±0.32
PCV (%)	45.92 ±0.44	41.84*** ±0.24	42.90 ±0.20	40.64** ±0.37	43.28 ±0.40	40.09*** ±0.61
MCV (fl)	64.38 ±0.65	72.37*** ±0.87	60.91 ±0.86	68.43*** ±0.64	62.64 ±0.46	68.15** ±1.49
MCH (pg)	19.45 ±0.32	20.52* ±0.15	18.64 ±0.06	20.04** ±0.05	18.88 ±0.28	19.87* ±0.19
MCHC (g/dl)	30.24 ±0.65	28.37 ±0.56	30.62 ±0.41	29.28 ±0.26	30.15 ±0.36	29.18 ±0.38

[a]Mean ± SEM, Student's 't' test ; *P < 0.05 ; **P < 0.01 ; ***P < 0.001

For other details, see Table II.

Biochemical analysis of blood

Table XIII depicts the effect of aldrin mixed diet administered for a period of 6-18 months on the various enzyme activities in blood. From amongst two phosphatases, AP was found to be the most sensitive one. This enzyme showed 2.3, 4.0 and 2.9 fold increase after 6, 12 and 18 months of aldrin feeding, respectively. The AcP, on the other hand, showed 97% increase at 6 month, but did not cause any significant deviation after prolonged aldrin feeding for 12 and 18 months. The SGPT activity was increased significantly by 197% after 18 months of aldrin feeding. The SGOT activity, on the other hand, showed significant increase of 102 and 47% after 6 and 12 months of aldrin administration, but showed 32% decrease during 18 months of aldrin feeding. The activities of LDH, ICDH, CPK and amylase were also drastically increased after aldrin feeding. As is obvious from Table XIII the LDH activity showed 129, 59 and 46.5% increase, ICDH activity 15, 57 and 33.5% increase and amylase activity 52, 8.5 and 40% increase over the respective controls after 6, 12 and 18 months of aldrin feeding. The ChE activity was raised 27% after 18 months of insecticide intoxication.

From amongst the several other biochemical components tested, the glucose, urea and protein contents increased, while FAA contents showed significant decrease when compared with the control serum. The bilirubin content decreased by 37% in the first 6 months of feeding but were remained unchanged during subsequent prolonged feeding. The choleserol content, on the other hand, were significantly lowered after aldrin feeding. The decline was maximum at 12 month toxicant feeding (Table XIII).

Biochemical analysis of liver

Table XIV shows the effect of long term feeding of aldrin on the hepatic enzyme activities. The various hepatic enzymes *viz.* AP, GOT, GPT, LDH and ICDH were raised after long term administration of insecticide. The increase in AP activity was 68, 71 and 76% after 6, 12 and 18 months of insecticide administration. The GOT activity was increased 44, 38 and 92%, while the GPT activity was increased 72, 62 and 16% when compared with the respective control activities. The LDH and ICDH activities behaved in the same manner. The LDH activity showed 31, 27 and 45% increase, while ICDH activity increased 68, 23 and 71% after 6, 12 and 18 months of aldrin feeding (Table XIV).

TABLE XIII : EFFECT OF FEEDING ALDRIN MIXED DIET (2.5 mg/kg body weight/day) FOR A TOTAL PERIOD OF 6-18 MONTHS ON THE VARIOUS BIOCHEMICAL COMPONENTS OF ALBINO RAT BLOOD SERUM.

Parameters	6 months aldrin feeding		12 months aldrin feeding		18 months aldrin feeding	
	Control (n=6)	Aldrin fed (n=4)	Control (n=4)	Aldrin fed (n=3)	Control (n=6)	Aldrin fed (n=4)
AP (KAU/dl)	9.57a ± 0.39	21.85*** ± 0.67	9.46 ± 0.68	37.92*** ± 0.99	10.21 ± 0.92	29.90*** ± 1.04
AcP (KAU/dl)	5.46 ±0.48	9.77*** ± 0.38	4.48 ± 0.25	4.99 ± 0.30	5 34 ± 0.59	6.09 ± 0.43
Amylase (SoU/dl)	242.53 ±16.74	368.57** ±22.43	210.29 ±10.57	288.11* ±15.82	202.03 ±12.22	283.48* ±23.65
ChE (RU/ml)	31.80 ± 3.76	27.17 ± 0.79	26.00 ± 1.85	29 83 ± 1.74	31.08 ± 1.82	39.35* ± 1.88
CPK (SiU/ml)	10.30 ± 0.77	31.92*** ± 2.64	7.57 ± 0.61	26.00*** ± 0.52	8.75 ± 0.97	30.62*** ± 1.86
ICDH (SiU/ml)	391.86 ±28.33	449.46 ±10.25	395.22 ±10.33	618.77*** ±11.16	462.53 ±24.13	617.22** ±23.03
LDH (IU/ml)	401.44 ±10.87	917.40*** ±21.37	442.20 ±49.62	692.73* ±43.55	509.49 ±27.82	746.64*** ±29.68
SGOT (IU/l)	21.02 ± 1.46	42.49*** ± 1.35	28.98 ± 2.73	42.66** ± 1.30	35.66 ± 2.55	24.31** ± 0.94
SGPT (IU/l)	17.72 ± 1.40	26.64 ± 4.14	14.82 ± 0.99	16.66 ± 0.66	18.75 ± 1.87	55.68*** ± 2.76
Bilirubin (mg/dl)	0.74 ± 0.05	0.47** ± 0.05	0.63 ± 0.03	0.68 ± 0.04	0.56 ± 0.04	0.66 ± 0.07
Cholesterol (mg/dl)	182.95 ± 6.25	161.54* ± 6.18	177.19 ± 5.21	104.66*** ± 5.15	180.12 ± 9.80	165.24** ± 5.07
Free amino acids (mg/dl)	9.27 ± 0.34	7.86** ± 0.17	9.00 ± 0.36	7.89* ± 0.07	11.09 ± 2.33	9.30 ± 0.23
Glucose (mg/dl)	114.76 ± 8.52	123.68 ± 5.85	107.4 ± 7.26	132.84 ± 7.04	124.57 ± 3.67	128.63 ±15.35
Protein (g/dl)	6.90 ± 0.37	8.75** ± 0.25	7.68 ± 0.21	11.07*** ± 0.33	8.58 ± 0.45	10.59** ± 0.16
Urea (mg/dl)	36.34 ± 2.20	44.27* ± 1.53	23.55 ± 2.84	39.73* ± 0.91	41.15 ± 1.91	59.58** ± 3.32

[a]Mean±SEM, Student's 't' test ; *P < 0.05 ; **P < 0.01; *** P < 0.001. For other details, see Table III.

TABLE XIV : EFFECT OF FEEDING ALDRIN MIXED DIET (2.5 mg/kg body weight/day) FOR A PERIOD OF 6-18 MONTHS ON VARIOUS HEPATIC BIOCHEMICAL COMPONENTS IN ALBINO RATS.

Parameters	6 months aldrin feeding		12 months aldrin feeding		18 months aldrin feeding	
	Control (n=6)	Aldrin fed (n=3)	Control (n=4)	Aldrin fed (n=3)	Control (n=6)	Aldrin fed (n=4)
AP (KAU/g)	0.74[a] ± 0.05	1.24*** ± 0.03	1.12 ± 0.07	1.91*** ± 0.09	1.08 ± 0.08	1.90*** ± 0.12
GOT (IU/g)	8.66 ± 0.54	12.48** ± 0.92	7.56 ± 0.46	10.41** ± 0.34	6.79 ± 0.23	13.05 ± 0.85
GPT (IU/g)	7.71 ± 0.68	13.29*** ± 0.46	5.02 ± 0.54	8.11** ± 0.43	6.05 ± 0.60	7.02 ± 0.49
ICDH (X 10^3 SiU/g)	33.29 ± 6.08	55.99** ± 2.57	49.49 ± 2.52	61.00** ± 0.91	42.50 ± 5.70	72.50** ± 1.77
LDH (X 10^4 IU/g)	58.29 ± 2.99	76.40* ± 4.53	54.25 ± 3.37	68.60* ± 4.00	44.60 ± 0.30	64.66*** ± 1.79
Cholesterol (mg/g)	5.97 ± 0.29	5.20 ± 0.80	9.01 ± 1.32	12.36 ± 1.81	10.50 ± 1.21	9.65 ± 0.21
Free amino acids (µg/g)	217.29 ± 7.70	171.19*** ± 4.01	197.98 ±14.18	170.12 ±11.62	226.70 ±13.24	203.33 ± 10.98
Glucose (mg/g)	30.87 ± 2.32	19.11* ± 3.64	27.12 ± 1.37	21.78 ± 3.10	38.32 ± 3.38	18.46 ± 1.93
Soluble proteins (mg/g)	124.92 ± 4.67	169.79** ± 7.94	135.22 ± 9.96	180.18** ± 1.73	159.00 ± 2.58	185.23** ± 5.41
Total proteins (mg/g)	216.96 ±13.05	159.27** ± 4.10	208.48 ± 6.70	294.20** ±12.88	227.60 ±11.88	241.50 ±12.57
DNA (mg/g)	3.05 ± 0.19	2.90 ± 0.37	2.54 ± 0.14	2.33 ± 0.42	3.06 ± 0.12	2.65 ± 0.40
RNA (mg/g)	9.68 ± 0.62	4.52*** ± 0.37	10.39 ± 0.31	5.74*** ± 0.42	11.30 ± 0.49	5.55*** ± 0.44

Mean ± SEM, Student's 't' test ; *P < 0.05 ; **P <0.01 ; ***<0·001. For other details, see Table III.

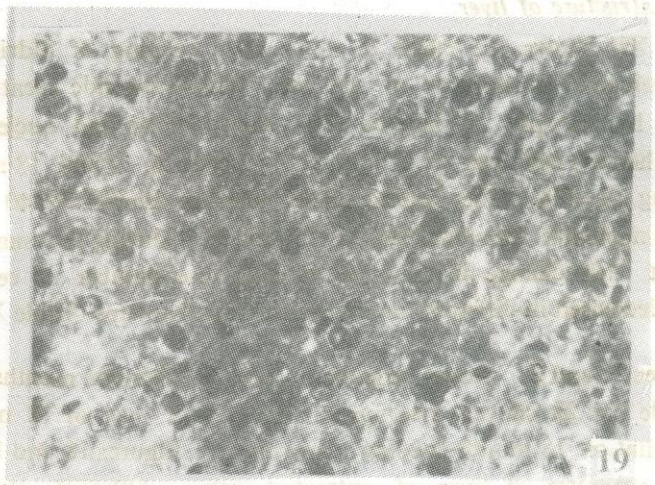
The changes induced by long term feeding of aldrin on the various biochemical components of rat liver, other than enzymes, are shown in Table XIV. The soluble protein contents increased after insecticide feeling. This increase was 36, 33 and 17% after 6, 12 and 18 months. The total hepatic proteins decreased 27% during the first 6 months, but showed 41 and 6% increase on further extending the insecticide administration for 12 and 18 months. The FAA contents conversely, showed a constant decrease of 21, 14 and 10% during this period. The glucose content likewise showed consistent lower values in insecticide treated liver. This decrease was 38, 20 and 52%. The cholesterol content remained statistically und affected through out the 18 months experimental period.

Both the nucleic acids contents were affected after aldrin feeding. The DNA, although showed lower values in insecticide treated groups, but these were statistically non-significant. The RNA content also decreased after insecticide feeding. This decrease was 53, 45 and 51% after 6, 12 and 18 months of aldrin feeding (Table XIV).

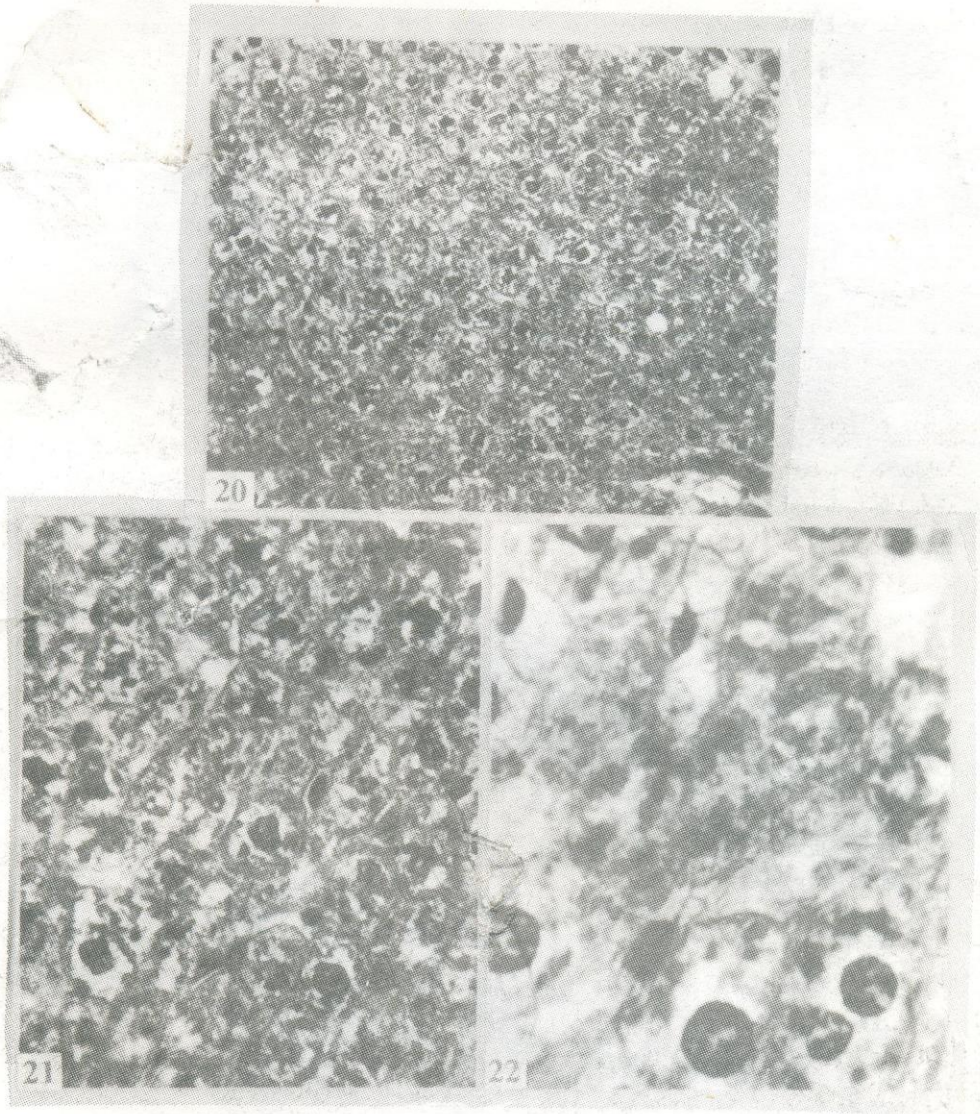
Histological structure of liver

Table XV shows the effect of long term feeding of aldrin on the various histological parameters of rat liver. The insecticide treatment was marked by hypertrophy of hepatic cells, their nuclei and nucleoli. An increase in hepatic cell was 48, 29 and 104% after 6, 12 and 18 months of aldrin feeding (n=90). The hepatic nuclei likewise showed 39, 40 and 70% increase and nucleolar size increased 11, 16 and 34% during the same period. Concomitant with change in the size of cells, the number of cells/microscopic field decreased in different insecticide treatment groups (Table XV).

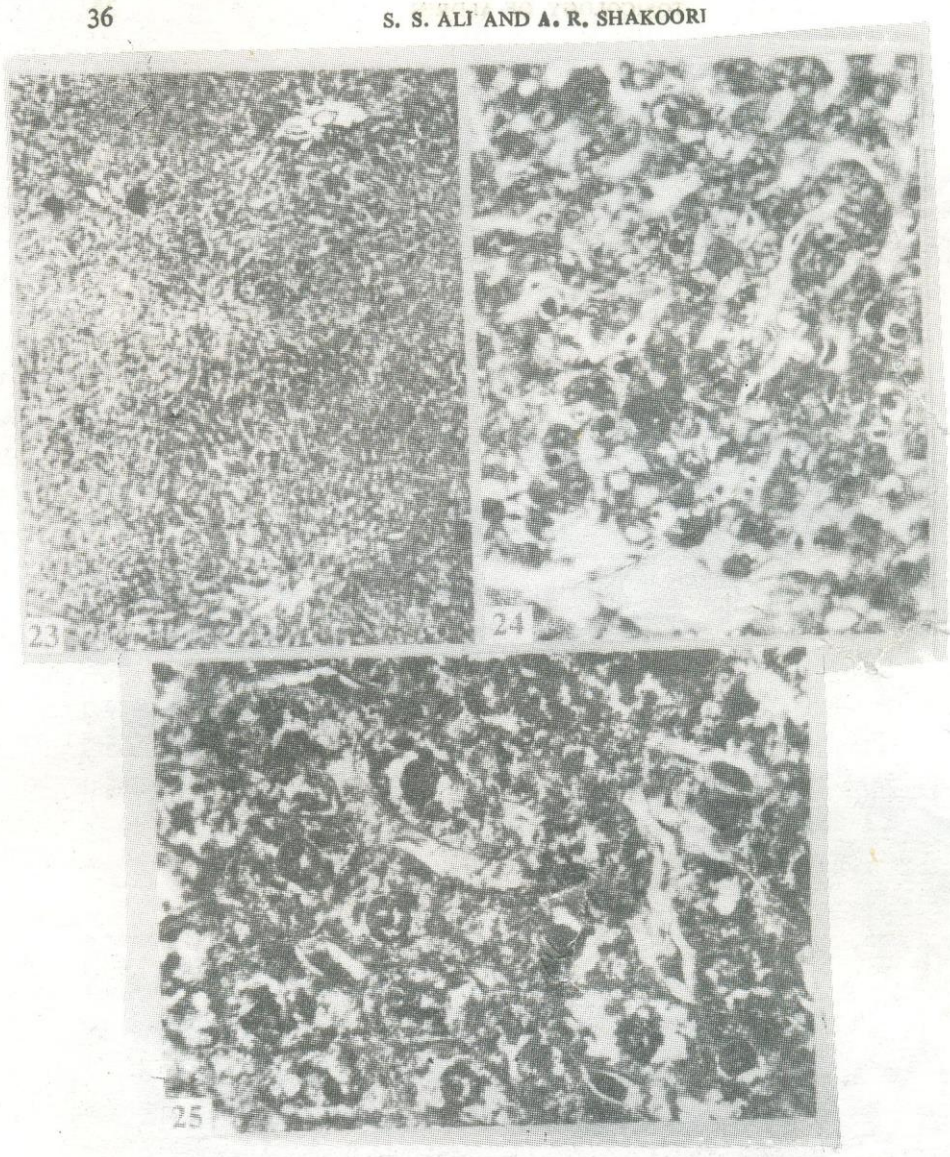
Figures 20 and 21 showed hepa ic structure after six months of aldrin feeding, while Fig. 22, showed histological structure of liver of 12 month and Figs. 23-24 that of 18 month feeding experiment. Figures 18 and 19 showed histological structure of liver of untreated rats. Although the general hepatolobular architecture is maintained throughout the experimental period, the hepatic cells were distinctly enlarged (Figs. 21, 22 and 24). Majority of the nuclei were converted into condensed bodies, and several darkly stained granules appeared in the cytoplasm, most of which were now marginated leaving clear spaces (=vacuoles) between the nuclei and marginal cytoplasm.



Figs.18-19
Histological structure of normal rat liver. Note the normal arrangement of hepatic cells and nuclei, kupffer cells and cords. Magnifications 18, 100X; 19, 200X. Stain: H&E.



Figs.20-22
Histological structure of rat liver fed on aldrin-mixed diet for 6 months (20,21) and 12 months (22). Note the cytoplasmic vacuolation as round the irregular nuclei (20,21) hypertrophied cells and nuclei (21,22). Magnifications: 20, 100X 21, 250X; 22, 500X. Stain: H&E.



Figs.23-25
Histological structure of rat liver fed on aldrin-mixed diet for 18 months. Note the disturbed lobular structure with atrophied zone (23), greatly increased sinusoidal areas with prominent kupffer cells, hypertrophied cells and nuclei (24,25). Magnifications:23, 25X; 24, 100X; 25, 250X. Stain: H & E.

TABLE XV : EFFECT OF FEEDING ALDRIN MIXED DIET (2.5 mg/kg body weight/day) FOR A PERIOD OF 6-18 MONTHS ON THE VARIOUS HISTOLOGICAL PARAMETERS OF ALBINO RAT.

Parameters	6 months aldrin feeding		12 months aldrin feeding		18 months aldrin feeding	
	Control	Aldrin fed	Control	Aldrin fed	Control	Aldrin fed
No. of cells/microscopical field (n=9)	277.29[a] ±11.74	184.73*** ± 8.46	249.31 ±13.79	171.22** ± 5.40	251.42 ± 9.68	164.81*** ± 7.24
No. of nuclei/ cell (n=90)	1.03 ± 0.03	1.09 ± 0.04	1.02 ± 0.03	1.07 ± 0.02	1.04 ± 0.01	1.05 ± 0.02
No. of nucleoli/ nucleus (n=90)	1.43 ± 0.10	1.91* ± 0.12	1.64 ± 0.11	2.17* ± 0.13	1.46 ± 0.07	1.73 ± 0.09
Size of cell (μ^2; n=90)	251.57 ±12.84	371.47*** ± 9.39	262.65 ±14.32	339.35** ±12.81	232.41 ±10.22	447.62*** ±15.81
Size of nucleus (μ^2; n=90)	40.23 ± 2.62	55.78** ± 1.77	38.54 ± 2.04	53.96** ± 1.87	46.54 ± 1.92	79.25 ± 1.76
Size of nucleolus (μ^2 ; n=90)	2.20 ± 0.35	2.44 ± 0.21	2.17 ± 0.26	2.51 ± 0.20	2.09 ± 0.31	2.79 ± 0.29

[a]Mean ± SEM, Student's 't' test ; *P<0.05 ; **P<0.01 ; ***P<0.001.

In several cases the nuclear shape was distorted which is a sign of nuclear degeneration (Figs. 20-24). Kupffer cells became extensively enlarged in almost all treatments (Figs. 22, 24, 25).

DISCUSSION

Body weight and liver weight

The body weight gain, in general, was reduced after aldrin feeding. In one short term experiment the rats were exposed to aldrin for 48 hours only, therefore no significant change in the body weight gain and RLW could be recorded. When aldrin was administered for 15 days and 18 months the body weight gain showed reduction, while RLW increased significantly. Several workers have concluded that action of aldrin and dieldrin is almost similar in animal systems, due to the fact that aldrin in living systems in converted into its epoxide, dieldrin (Ghiasuddin and Menzer, 1976 ; Wolff *et al.*, 1980; Kurihara *et al.*, 1984; Long *et al.*, 1986). The decrease in body weight gain after administration of insecticides was frequently reported (Argyle *et al.*, 1975; Blus, 1978 ; Shakoori *et al.*, 1984). However, Fitzhugh *et al.* (1984) did not observe any change in growth of rats fed 0.5-150 ppm aldrin for 2 years. The reduction in weight gain is an important indicator of metabolic abnormalities inside the body due to effect of certain toxicant. In this case the energy requirement of the body may be increased for the induction of body's defence mechanism to detoxify the toxicant compound. Under these circumstances first fat and then protein may be mobilized to fulfil the body needs which may result in reduced weight gain. Increase in RLW showed liver enlargement (hypertrophy) which is a typical response of liver to foreign toxic compounds (Fitzhugh *et al*, 1964; Virgo and Bellward, 1975; Wright *et al.*, 1978; Singh *et al.*, 1985).

Haematological studies

All the haematological parameters tested behaved exactly in the same way, irrespective of the dose and duration of aldrin administration. The Hb content and RBC count decreased in all experiments. The Hb content decreased 11-12% in short term experiment I, 8-12% in short term experiment II and 9-14% in long term experiment. The RBC count decreased 14% in short term experiment I, 10-22% in short term experiment II over a period of 3-15 days and 15-18% in long term

experiment over a period of 6-18 months. The insecticide treatment has repeatedly been found to cause a decrease in Hb content and RBC count (Ali and Shakoori, 1981 ; Shakoori and Ali, 1982 ; Shakoori *et al.*, 1988). The decreased synthesis of Hb and slower activity of haematopoietic tissue under the influence of aldrin may explain the low values of Hb and breakdown of RBC. Bhatnagar *et al.* (1980) has shown that more than 75% workers in a pesticide factory were anaemic. Qayyum and Shami (1983) has reported that 5, 50 and 100 ppm aldrin treatment to fish produced a decline in erythrocyte count, Hb concentration and haematocrit (PCV) values. Decreased Hb, PCV and RBC count occurred after 1.0 ppm dieldrin feeding for 2 years (Walker *et al.*, 1969). The PCV, on the other hand, remained unaffected in short term experiment I, and until day 9 in short term experiment II, when it was decreased 3% and further falls down to 6% after 15 days of aldrin feeding. In long term experiment the PCV decreased 5-9% over a period of 6-18 months. This decrease in PCV may be attributed either to decreased cellular content and or increased liquid (plasma) content, mainly the water. Leukocytic (WBC) count shows typical response to insecticide treatment. This count was raised in all experiments but increase was prominent in both short term experiments which was 25-28% in 48 hours experiment, and 19-45% in 3-15 day feeding experiment. In long term experiment the WBC count showed 11% significant increase, after 12 months of aldrin feeding which is comparatively a little change. The MCV and MCH values increased under all experimental conditions. The increase in MCV was 13% after feeding 20 mg aldrin/kg body weight for 48 hours, while it was 10-21% in the second short term experiment. In long term experiment the increase in MCV ranged between 9-12%. The MCH showed maximum increase (6-13%) in 15 day feeding experiment, while this increase in 48 hours feeding experiment was 3-4% and in long term feeding experiment it was 5-8%. The MCHC was nonsignificantly decreased in long term experiment, but was decreased significantly (8-9%) in the first short term experiment and 6-7% in the second short term experiment. The patterns of changes in MCH, MCV and MCHC suggest that anemia produced by aldrin intoxication was macrocytic and hyperchromatic type.

Blood serum chemistry

Under hepatotoxic conditions, which normally ensue after aldrin treatment, the enzymes of hepatic cell apparently tend to leach out and

accumulate in the blood for some time, until they were cleared from the blood by further metabolic process or degradation (Krample and Hladka, 1975). Almost all the enzymes tested in the present studies were elevated except for ChE and ICDH, which behaved differently under different experimental conditions. In short term experiment, when aldrin was administered @20 mg/kg body weight for 48 hours, all enzymes showed elevated activities except for SGPT, which remained unaltered. The amylase and CPK activities were not significantly deviated after 24 hours of feeding, but showed 60% and 31% increase respectively, after 48 hours of aldrin feeding. From amongst other enzymes, SGOT showed maximum increase *i.e.* 100% and 37% after 24 and 48 hours of insecticide feeding. This increase in AP activity was 51% and 141%, in AcP it was 26% and 15%, in LDH it was 46% and 78%, in ICDH it was 61% and 135% and ChE activity was increased 58% and 88%, respectively in 24 and 48 hours feeding experiments.

In the second short term experiment, in which a dose of 8 mg/kg body weight/day was administered for 15 days, all the enzymes generally demonstrated the same trend, as in the first experiment, except for ChE which did not indicate any change at this dose. Of all the enzymes tested AP, AcP, SGOT, LDH and amylase activities increased tremendously. The amylase activity was increased 36% after 3 days and 109% after 15 days of continuous feeding. The AP activity increased 94% after 3 days of feeding and increased 368% after 15 days of feeding. The AcP activity increasd 115, 194, 256, 142 and 105% after 3, 6, 9, 12 and 15 days of aldrin feeding. The SGOT activity was not affected until day 9, when it showed 137% increase, and which shot upto 195% after 15 days of continuous feeding. The SGPT activity, which was not altered in the 48 hour feeding experiment, increased 88%, 117%, 73% and 75% after 3, 6, 9 and 12 days of feeding. The LDH activity increased 39% after 3 days and 115% after 15 days of feeding. The ICDH activity, on the other hand, was decreased, respectively, 41, 40, 11, 23 and 22%, after 3, 6, 9, 12 and 15 days of insecticide feeding. The CPK activity increased 83 and 53% after 9 and 12 days of aldrin feeding.

In the long term experiment the extent of elevation of enzyme activities was not of that level as in short term experiments except for CPK activity, which increased 3.1 fold, 3.4 fold and 3.5 fold after aldrin feeding. Like short term experiments, the activities of all the estimated enzymes elevated after

aldrin feeding. The amylase activity increased 40-52% after 6-18 months of feeding. The increase in AP activity was 2.3 fold, 4 fold and 2.9 fold, while in AcP this increase was 97%, 11% and 15% after 6, 12 and 18 months of feeding, respectively. Both transaminase activities likewise raised. This increase was 102, 47 and 32% for SGOT and 50, 12 and 197% for SGPT after 6, 12 and 18 months of aldrin feeding. The LDH activity also increased significantly, while the increase in ICDH activity was 57% and 33% after 12 and 18 moths of insecticide feeding. The ChE activity was raised (27%) only after 18 months of continuous feeding.

The raised enzymatic activity, especially of liver function was therefore, direct indicator of disturbed liver function (Fitzhugh *et al.*, 1964 ; Gertig *et al.*, 1971 a; Shakoori *el al.*, 1984, 1988). The response of all these doses of aldrin on the activity of blood serum enzymes has been fairly uniform. Although aldrin was metabolized in the liver into dieldrin (Ghiasuddin and Menzer, 1976 ; Wolff *et al.*, 1980), the sensitivity of different enzymes to aldrin treatment has been clearly manifested in these experiments. In dieldrin treated groups, the CPK activity was not seriously altered in both short term experiments and remained unaltered in long term experiment, while a distinct increase has been reported in the case of aldrin-treated blood serum which was an indicative of some kind of muscular damage or degeneration. The CPK activity, therefore, was inhibited or has a tendency to be inhibited by dieldrin (Williams and Casterline, 1970; Hendrickson and Bowden, 1976; Meany and Pocker, 1979). The SGPT activity likewise was not drastically affected in short term experiment I, and has no effect in the case of long term experiment with dieldrin. However, increase was significant until day 12 in second short term experiment. So in aldrin feeding the SGPT activity was comparatively less affected.

Gertig *et al.* (1971b) reported increase in both transaminases (SGOT and SGPT) in human serum after aldrin feeding, while in porcine serum only SGPT was elevated and SGOT was inhibited. Gradual increase in SGOT and SGPT activities after aldrin intoxication in goats at different dose levels was also observed by Singh *et al.* (1984, 1985). Both phosphatases (AP and AcP) prominently increased in both short term and long term experiments, except that AcP at 12 and 18 months of aldrin feeding which remained unaltered. Alkaline phosphatase is an important enzyme in the body and it takes part in the number of physiological activities like splitting of various phosphate esters at

alkaline pH, transphosphorylation and protein synthesis. So alterations in its activity indicate wide range of metabolic abnormalities in the body. Elevated AP, AcP and glucose 6-phosphatase activities in fish with peak values at 20 days exposure were reported (Gupta and Dhillon, 1983). Acid phasphatase is a lysosomal enzyme and increased in response to cell damage or cell death. In injured tissues its increase indicates a prenecrotic change. Cholinesterase activity increased in short term experiment I and at 18 month feeding period in long term experiment, while decreased in short term experiment II at 3 day feeding level. Significant inhibition in ChE activity was also reported with aldrin and other pesticides by Bhatnagar *et al.* (1980) and Basol *et al.* (1984) in pesticide factory workers and other animals. Irrespective of the change, the alteration in ChE activity produce a lack of co-ordination in the metabolic pathways and variety of other symptoms in animal systems (Srivastava and Singh, 1981). The activity of other enzymes have the same pattern as observed with dieldrin, (Shakoori and Ali, 1989). The only exception was ICDH activity which was significantly lowered in the short term experiment II and elevated in other experiments, while in dieldrin treatment the ICDH activity showed a regular increase in all experiments. This indicated that aldrin in this experiment affects the mitochondrial oxidation in different ways than dieldrin. However, further experimentation is required to confirm is statement. Increase of hepatic enzyme activities under the influence of aldrin has also been reported with reference to several other enzymes, other than being reported here for LFT. Anastasi and Bannister (1980) have reported that aldrin stimulated mitochondrial enzymes like muscle pyruvate kinase, LDH and malate dehydrogenase, but inhibited mitochondrial enzymes like cytochrome oxidase in fish.

Besides various enzymatic activities, other biochemical components of blood serum have also been variously affected by aldrin treatment. The bilirubin content decreased in short term experiment I and in long term experiment at 6 months treatment, while showed significant increase in 15 day treatment. However, the pattern showed the signs of recovery in this 15 days aldrin feeding experiment. Increase in bilirubin was also reported by Enan *et al.* (1982). The glucose also behaved differently in different treatments. It showed increase in 48 hours treatment and at 6 and 12 month treatment after strong and weak dose administration, while decreased in the 15 days experiment.

The peak value was observed at 9 days of continuous aldrin feeding after which the content decreased gradually until day 15. So the aldrin treatment at different dose levels and durations produced hyperglycemia as well as hypoglycemia. Liver and muscle glycogen and blood glucose was reduced at 0.01 % aldrin concentration within 1st 30 days of administration (Mahajan and Sharma 1984). Bilirubin demonstrated similar type of behaviour. The significance of this irregular hebaviour of glucose and bilirubin after aldrin intoxication was not clearly understood. Srivastava and Singh (1981) reported the hypo - and hyperglycemia in the same group of experimental animals at different treatment durations at one dose level. It was not confirmed that if the aldrin has different mechanism of action under different conditions of dose and duration. The FAA and cholesterol contents decreased in almost all aldrin feeding experiments. Similar findings were obtained in dieldrin feeding experiments (Ali and Shakoori, 1988). The cholesterol content, although showed a decrease in 15 day aldrin feeding experiment but it was non-significant. The decrease in FAA content revealed either their incorporation in the protein or their utilization as energy source through glouconeogenesis and other processes. Considerable variation was found in serum cholesterol and protein contents after insecticide feeding @ 0.1-1.0 ppm (Bano, 1982). Decrease in serum cholesterol level in the present study may be due to decreased synthesis which in turn may be due to the defficiency of precursor compound (acetyl co-enzyme - A) partly in the glucose deficient environment and partly due to extra needs of energy for the body to detoxify the toxic compound. The increase in urea content in our results was possibly reslut of enhanced amino acid catabolism for energy needs of the body. Enan *et al.* (1982) have also found similar results in rats treated with different chlorinated compounds. Protein content of the serum also remained elevated in all experimental condition. This condition indicated liver cell damage (Enan *et al.*, 1982) in which excess of globulin was released by the liver cells (Varley *et al.*, 1980). Gluth and Hanke (1985), however, did not show any increase in serum protein contents of fish after aldrin intoxication but on the other hand they showed significant decrease in protein and cholesterol contents which was most prominent in the later part of the experiment rather then the initial. Skalsky and Guthrie (1977) have also shown binding of dieldrin with proteins of rat blood. According to Iatropoulos *et al.* (1975) the dieldrin is quickly absorbed and transported to the liver of Sprague Dawley rats. Only a portion is metabolized and excreted. The major portion is redistributed and stored in adipose tissue.

Liver biochemistry

The changes in the parameters of liver function tests are actually reflection of changes in the liver structure and chemistry (Ali and Shakoori, 1981 ; Shakoori *et al.*, 1982, 1988 ; Shakoori and Haq, 1987 a, b). All the hepatic enzymes tested showed raised activities after aldrin treatment. In short term experiment I, in which aldrin @ 20 mg/kg body wieght was administered for 48 hours, the GOT, GPT and LDH activities were not affected until 48 hours, when all their activities increas 28%, 40% and 26% after aldrin treatment. The AP activity appeared to be more sensitive and was increased 69% and 17% after 24 and 48 hours of aldrin feeding. The ICDH activity was not affected at all.

In the second short term experiment the ICDH activity was considerably increased by 121%, 56%, 132%, 142% and 100% after 3, 6, 9, 12 and 15 days of feeding @ 8 mg/kg body weight/day for 15 days. AP activity was drastically increased, which was 80, 73, 133, 144 and 162%, respectively, after the same durations of aldrin feeding. The GPT activity was not significantly altered. while hepatic GOT activty showed 14, 97, 186, 76 and 171% increase after 3, 6, 9, 12 and 15 days of aldrin feeding. The LDH activity was also significantly increased after 9 and 12 days of insecticide administration.

In long term experiment the activities of all hepatic enzymes were significantly increased. The raised enzymatic levels in blood are attributable to liver damage under pathological conditions, while their low levels in blood could either be because of great regenerative power of liver as a result of which leaching out of the enzymes in blood serum becomes minimal, or due to the biosynthetic activity which implies routing of all the biochemical components towards this activity (Rosen and Nichol, 1963 ; Knox and Greengard, 1965; Bhatia *et al.*, 1972b, 1973) in liver. The raised enzymatic activities in the liver, on the other hand, may be due to induction of enzyme synthesis (Street, 1969 ; Kimbrough *et al.*, 1971; Krample and Hladka, 1975), while their low levels could either be because of enzymatic inhibition (Hendrickson and Bowden, 1976 ; Meany and Pocker, 1979) or due to liver damage without any regeneration.

Besides various enzymatic activities several other biochemical components of the liver were considered to ascertain hepatotoxicity. The cholesterol

content decreased under all circumstances. In short term experiment I, the cholesterol content decreased 29%, while in 15 day feeding experiment the decrease was 66-72% after 3-15 days of feeding. When feeding of aldrin was extended for 6-18 months, the cholesterol content remained unchange. The decrease in cholesterol in both short term experiments was also reflected in the blood. Decreased cholesterol in both blood and liver gave the idea that aldrin feeding generally lowered its synthesis at least in existing conditions of dose and duration. At the same time, the increased rate of excretion can not be ruled out. The glucose content behaved differently under different experimental conditions. In short term experiment the glucose content decreased 43%, while in long term experiment a decrease of 38-52% was recorded. In 15 day feeding experiment the glucose content showed a gradual increase after aldrin feeding. The FAA content, likewise behaved almost in the same way when compared with glucose. Thc increase in glucose and FAA in 15 day aldrin feeding experiment indicated either decreased utilization or increased rate of their synthesis. The soluble protein contents were not altered in 15 day feeding experiment, while about 29% increase was found in short term experiment I and in long term feeding experiment. A distinct increase in the total hepatic protein content was observed under all experimental conditions. The decreased cholesterol level, increased glucose and altered FAA contents were indicative of hepatotoxicity and corrective measures to acquire more energy by raising level of glucose and increased protein synthesis. The increased hepatic soluble proteins alongwith serum protein in short term experiment I and in long term experiment confirmed that protein synthetic activity of liver also increased perhaps for regeneration purposes after insecticidal damage. The nonsignificant increase in hepatic proteins in 15 day experiment may be due to hepatic injury with out regeneration. The increase in total liver proteins was responsible for increased liver weight after aldrin intoxication. Increase in liver total protein after dieldrin feeding was reported by Wright *et al.* (1978) which according to him was due to increase in microsomal and soluble fractions.

Nucleic acids content

The DNA content remained unaffected after aldrin treatment, while the RNA content increased following 15 days of feeding aldrin mixed diet @8 mg/kg body weight/day. This increase was 50, 67, 92, 158 and 113% at

3, 6, 9, 12 and 15 days of feeding. In the long term experiment, however, the RNA content decreased 51-53% after 6-18 months of aldrin feeding. The increased RNA content should eventually lead to increased protein content, while its decrease indicated disturbed transcription process or rapid breakdown of RNA. This probably originates from hepatic necrosis, which is also indicated by raised enzymatic levels in blood serum due tocell damage. In dieldrin treated rats also, the DNA content resists the effects of the insecticides, while the RNA content increased at the same time (Shakoori *et al.*, 1982). Hall (1980) has studied biological interaction of aldrin with the nuclear DNA of human fibroblasts. Rocchi *et al.* (1980) studied action of aldrin on DNA synthesis with a short term *in vitro* system using rat thymocytes and found that it does not induce damage to human lymphocyte DNA. In swine kidney cells (IBRS 2 cells) the cellular protein, RNA and DNA content decreased, when exposed to 0.1-100 μg/ml of aldrin (Rodrigues and Puga, 1979).

Liver histology

All the above biochemical findings are reflected in the liver histological structure due to chemical toxicity. The appearance of vacuoles and hypertrophy of cell and its inclusions are the typical signs of hepatotoxicity. Inspite of the fact that biochemical state predicts mild necrotic region, this is apparently not substantiated by the histological studies. Singh *et al.* (1985) did not find any severe pathology in the liver of goats fed aldrin for 21 days except some disorganisation of cells around the central vein. Histopathological changes induced by aldrin (10-25 ppm) were characterized by damaged cells, vacuolar degeneration of their cytoplasm, localized necrosis, parenchymal degeneration and nuclear displacement (Mathur *et al.*, 1981). These results are also in agreement with the results reported in this study.

Although the number of nuclei/cell and number of nucleoli/nucleus were not drastically altered, but the size of hepatic cell, its nucleus and nucleolus increased considerably. The hypertrophied cell, its nucleolus and nucleus is a typical response of hepatic cells to xenobiotics exposure. Moderately increased vacuolation, enlarged centrolobular hepatic cells were also shown by 50-100 ppm aldrin feeding (Fitzhugh *et al.*, 1964).

The carcinogenic potential of aldrin in mice, which has so frequently been reported in the previous literature (Davis and Fitzhugh, 1962; Fitzhugh *et al.*, 1964; Reuber, 1975, 1976, 1977; David, 1979) was not seen in the present studies.

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