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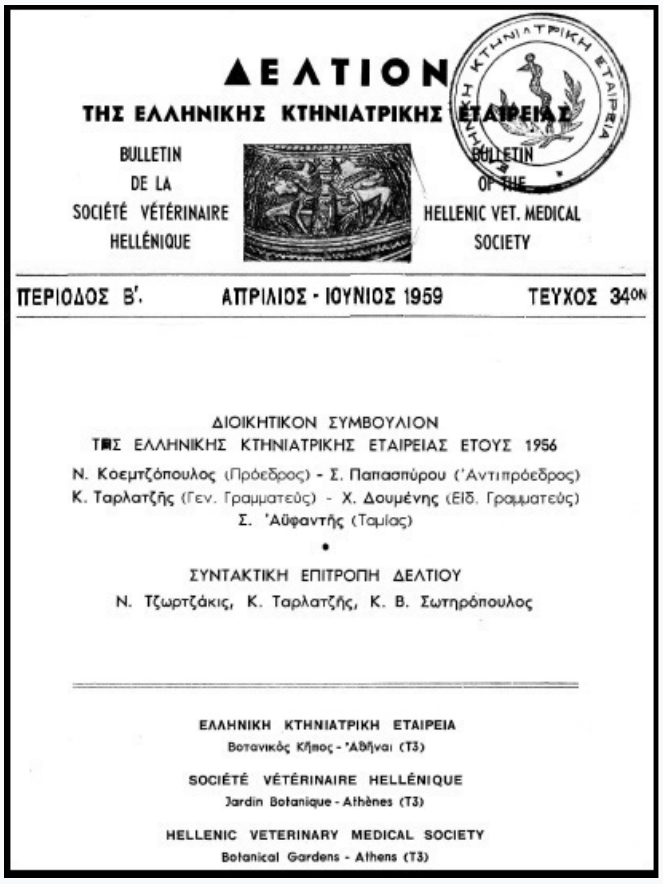

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THE EFFECT OF 1,1-DICHLORO-2,2-BIS (P-CHLOROPHENYL) ETHANE (DDD OR TDE) ON THE ADRENAL CORTEX OF G0ATS

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Ὁ ἐκλεκτὸς καὶ διαπρεπὴς συνάδελφος κ. Β. Χατζήολος, Καθηγητὴς τοῦ Πανεπιστημίου τοῦ Maryland, ὑπείκων εἰς παράκλησιν ὑποβληθεῖσαν αὐτῷ κατὰ τὴν ἐνταῦθα πρόσφατον παραμονήν του, ἐδέχθη νὰ συγγράψῃ τὴν κατωτέρω μελέτην ἀποκλειστικῶς διὰ τὸ Δελτίον μας.

Ἡ Συντακτικὴ Ἐπιτροπὴ φρονεῖ ὅτι ἐκπροσωπεῖ τὰ αἰσθήματα πάντων τῶν συναδέλφων ἐκφράζουσα πρὸς τὸν ἀγαπητὸν συνάδελφον ὅστι τιμᾷ τὴν Ἑλληνικὴν πατρίδα εἰς τὴν ξένην, τὴν βαθυτάτην της εὐγνωμοσύνην.

THE EFFECT OF 1, 1-DICHLORO-2,2-BIS (P-CHLOROPHENYL) ETHANE (DDD OR TDE) ON THE ADRENAL CORTEX OF GOATS

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DDD, like suramin sodium [14] produces severe cytotoxic atrophy of the zona fasciculata, or toxic involution of the adrenal cortex, in certain animals, particularly in dogs, when administered over prolonged periods [7,20-26,28] However, reports on the effect of this agricultural insecticide, an analogue of DDT, on the adrenal cortex of small laboratory animals are inconclusive. Some researchers working with DDD on adult rats observed histological damage, or assumed, on the basis of eosinophil response, uric acid/creatine ratio, insulin sensitivity [2,32] and decreased response to cold stress [4] that adrenal disfunction had occurred. Other researchers did not observe degeneration of the zona fasciculata or adrenal cortical atrophy in similar experiments on rats, mice, and rabbits.[6,7,10,17,21,30]. Experiments with DDD on monkeys showed no adrenal damage.[21]

When used on patients showing Cushing's syndrome, DDD pro-

duced no significant clinical effect on the condition, nor did it induce any recognizable biochemical or histological response.[29]

The present paper reports the effect of this compound on the adrenal cortex of the goat and is based on an analysis of clinical manifestations, blood examination, and, primarily, histophathologic changes of the adrenal cortex during various periods of administration of the drug. An abstract of these findings has been published.[13]

MATERIALS AND METHODS

Ten goats of various ages (three months to three years) were used. Eight were administered DDD per os in gelatin capsules in doses varying from 100-280 mg/kg over periods ranging from 6 to 65 days (Table I). In order to avoid shock, the dose was increased progressively each week in accordance with the animal's physical condition and resistance to the drug. One goat which was killed within twenty-eight days had received an intramuscular injection of 100 mg of cortisone on the twenty-fourth day of DDD administration. Two of the goats were used as control animals.

Blood samples taken from the jugular vein were examined by the usual laboratory procedure. Smears of bone marrow were stained by Wright and Giemsa techniques.[19]

Autopsy was performed immediately after the death or slaughter of the goat. The adrenals were weighed ; specimens from them and from other organs were fixed in 10 % formalin and in Zenker's and Bouin's fluids for sectioning. Some frozen sections of the adrenal were stained for lipids with Sudad IV, oil red 0 and Nile blue, and others were treated according to Schultz's method for cholesterol [19] and according to Albert's and Leblond's technique for plasmalogens.[1],[31]. Paraffin sections of adrenals were stained according to (1) Mallory's acid fuchsin, (2) Van Giesson's picric acid and acid fuchsin, (3) Heidenhain's aniline blue, (4) Masson's trichrome, (5) Foot's modification of Beilschowsky's stain for connective tissue, collagen and reticulum, and (6) Wolbach's modification of Giemsa's stain for differentiation of myeloid elements.[16],[19] Paraffin sections of the pituitaries were also stained by various techniques :

(1) Periodic Acid-Schiff [16] (2) a modification of Mallowry's Azan by Gilmore's et al,[9] and (3) Halmi's for A, B, C, and D-cell differentiation.[12]. Routine parrafin sections of the other organs were stained with hematoxylin-eosin.

RESULTS

Clinical manifestations: Those goats which withstood prolonged treatment with DDD showed no signs of physical discomfort during the early stages of the administration of this drug. However, toward the end, approximately ten days before death, these animals exhibited shaggy hair and suffered loss of weight. Later, their appetites became poor or capricious and general weakness appeared. Their gait was staggering and their stance painful. Neuromuscular manifestations and abnormal postures (horizontal position of the head, loss of orientation and equilibrium) appeared thereafter. The loss of subcutaneous adipose tissue revealed enlarged and swollen lymph nodes. Shortly before death, the animals appeared to have been stricken with paralysis.

The injection of cortisone to one animal shortly after the onset of clinical manifestations produced immediate but temporary results. Two days later the symptoms reappeared with more intensity and death followed within a few days.

In the goat which died suddenly, the autopsy revealed meningeal hemorrhages in the posterior part of the cerebral floor.

Blood picture: During the period of DDD administration, the blood picture varied, apparently in relation to the progress of cortical destruction. At the beginning the circulating eosinophils and lymphocytes remained under 48 and 10 per cent respectively, but toward the end they rose above the initial levels. A typical picture of the variation of the blood elements of the goat which survived the longest period of DDD administration is presented in Figure 1. Thus, a certain degree of eosinophilia and lymphocytosis prevailed during the late phase. A few lymphoblasts were found in the blood smear of one animal. In addition, the number of erythorocytes, the hemoglobin percentage, the hematocrit values, and the blood sugar decreased progressively. Bone marrow smears revealed an increase of cellular elements of the lymphoblastic series.

Adrenal changes: Macroscopically the adrenals exhibited changes in size and color. Adrenals of goats in Group 1 to which DDD was administered for a long period weighed less than those of goats in Group 2 to which DDD was administered for a short period with the exception of the adrenals of one goat which were noticeably enlarged owing to hyperplasia of lymphatic tissue in the parenchyma. The relative weight of the adrenals per pound of body weight

averaged 58.8 mg. for the first group and 79.6 mg. for the second group, as compared to 68.2 mg for the controls (Table 2).

Eliminating the goat which showed lymphoid metaplasia, the average relative weight of the adrenals of the other three in the first group was 46.8 mg/lb of body weight.

Specifically, the adrenals exhibited the following changes: One week after DDD administration, the adrenals were slightly enlarged

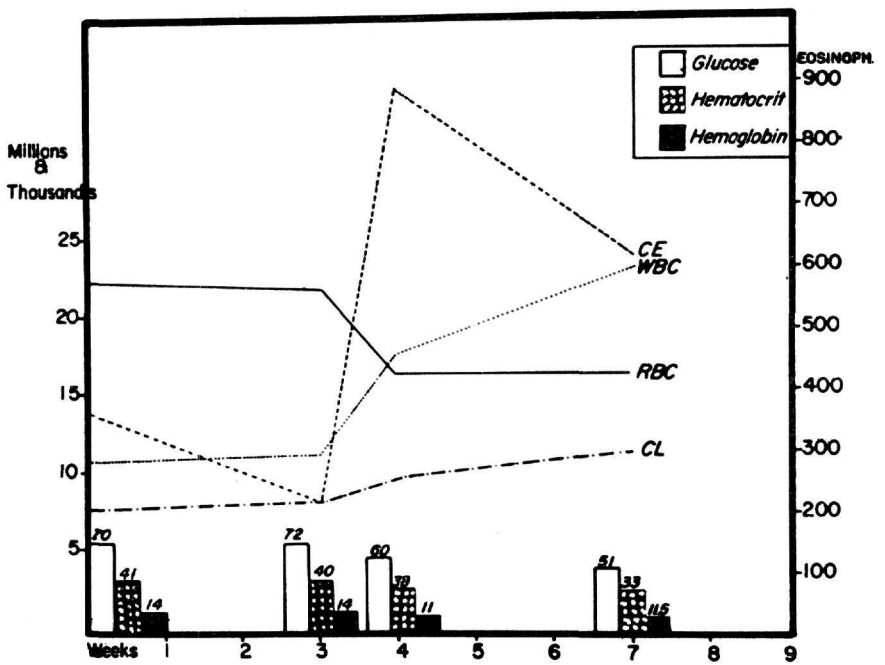

Fig. 1. Blood picture of a young goat during DDD administration indicating progress of cortical destruction; (C.E.=circulating eosinophils, W.B.C.=white blood cells, R.B.C. = red blood cells, and C.L.=circulating lymphocytes).

and discolored with a few grayish-white and dark red spots. In cross sections the cortex showed a ratio of approximately 1.8:1 with the medulla. Microscopically the subcapsular zone appeared to be thickened and the glomerulosa enlarged. The cells in the outer fasciculata were large and showed numerous lipid droplets which stained bright red with Sudan IV and oil red 0 and deep purple with Nile blue. Congestion, scattered tiny hemorrhages, and a few small necrotic foci were noted in the inner zones and particularly in the zona reticularis in which scattered small foci of lymphocytic infiltration were

also observed (Fig. 1-4, Plate 1). The medulla was noticeably enlarged and showed hemorrhages, cell degeneration, and eosinophilic infiltration in the clusters.

Three weeks after DDD administration, the adrenals appeared to be reduced in size. The ratio of the cortex to the medulla was 0.8 : 1. The capsule was broadened and had numerous small adenoma-like nodules. The glomerulosa was enlarged and uniform in thickness. The loops showed large cells with thin to medium lipid droplets. The cells adjacent to the junction of the zona fasciculata and glomerulosa were hyperchromatic and the capillaries distended. The zona fasciculata was narrow and was formed by distorted columns. Scattered cortical cells had a signet-ring appearance due to lipid accumulation. Here the necrotic foci were dispersed and scattered groups of lymphoid or undifferentiated cells infiltrated the area. Centripetally, the infiltration became diffuse and some myeloid elements, in addition to common leukocytes, were detected.

In addition lymphoid nodules of various sizes (Fig. 5, Pl. 1) and eosinophilic infiltration were noted in the area adjacent to the medulla. This infiltration often extended into the medullary clusters, which showed degeneration.

Four weeks after the beginning of DDD administration, the adrenals were discolored and mottled with small whitish spots. Microscopically, the glomerulosa was enlarged, occupying one-third of the cortex. The cells in the loops were large and loaded with unevenly distributed medium-sized lipid droplets which stained light purple with Nile blue. The cells adjacent to the fasciculata (sudanophobic zone) showed prolifertation. The rest of the cortex was reduced and disorganized. Scattered spots of fatty metaplasia were noted, whereas the necrotic spots appeared to be larger (Fig. 6, Pl. 1). The accumulated lipids showed qualitative changes, namely negative Schultz's and Feulgen's reactions for cholesterol and plasmalogens, respectively. The sisusoids were engorged and scattered keukocytes infiltrated the area. In the inner fasciculata most of the cortical cells were atrophic or necrotic and the zone lost its architectural identity. Here numerous large foci of lymphocytic infiltration and some lymphoid nodules were present surrounded by areas of fatty metaplasia. Neutrophils, and more often eosinophils. were at the periphery of the nodules. Scattered plasma cells and some erythroblasts and other myeloid elements in mitosis were observed among the degenerated cells. A number of structures with concentrated layers, believed to

be amyloid bodies, were found in the inner fasciculata (Fig. 4, Pl. 2). The sinusoids were distended and often formed luminal - like dilatations. In many places the stroma was dense and formed large bands. The zona reticularis showed numerous large lymphatic nodules.
The medulla was enlarged and congested. The peripheral clusters were enlarged, but thinned out and often infiltrated with leukocytes. Degeneration of the chromaffin cells in the center was common. Cortical islands in the medulla exhibited lesions similar to those noted in the cortex.

Nine weeks after the beginning of DDD administration, the slightly enlarged adrenals exhibited grayish spots. Microscopically, the ratio betwen the cortex and medulla was 1.6 : 1 ; the demarcation line was inconspicuous. The zona glomerulosa was enlarged and conspicuous and showed scattered adenoma - like nodules at the periphery. Some of the loops, formed by crowded cells, were large. Characteristic also was the increased lipid material in the cells, some of which had a signet - ring appearance, and the presence of lymphocytic foci which were reminiscent of small lymph-nodules (Fih. 1, Pl. 2). Scattered neutrophils were present. In certain areas the stroma mas increased and the capillaries enlarged. The rest of the cortex was reduced and its architecture had lost its identity. The outer fasciculata showed scattered areas of lipoid metaplasia, or proups of cells with a signet-ring appearance among the distorted cords. Centripetally, an extensive and diffused lymphocytic infiltration was present (Fig. 2, Pl. 2). In many places the lymphocytes were thickly settled and formed large nodules. They showed germinal centers with numerous mitotic figures (Fig. 5, Pl. 2). Occasional cortical cells, less involved in the degenerative process, showed mitotic figures or bilobed nuclei with prominent nucleoli.

The capillaries had thickened walls and some showed hyalinization. The sinusoids were distended and numerous, but did not show marked luminal - like formations. The endothelial cells were prominent and numerous. Fibroblasts and winding bundles of fibers formed a streghened stroma (Fig. 6, Pl. 2). Neutrophils were scattered about. In the zona reticularis, which fused with the fasciculata, a syncytial cell formation has common, in addition to a large lymphoid nodule formation (Fig. 3, Pl. 2). The few remaining cells showed vacuolization or reticulization. The medulla exhibited changes similar

to those mentioned previously in the animals treated for four weeks with DDD.

The main histopathologic changes in the other organs included: General hypertrophy and hyperplasia of the lymphopoietic organs and of the lymph follicles wherever they are normally found ; increase in number and size of the beta cells and scattered pyknosis of the alpha cells of the pituitary. In additiod, goats 544 and 568 exhibited mild fatty changes and centrilobular necrosis in the liver ; mild subchronic glomerulonephritis with degeneration of the epithelium of the convoluted tubules in the kidney ; fatty changes, hyalinization, and scattered inflammatory foci of the heart ; desquamation of the oesophageal epithelium ; congestion, small erosions and distention of the abomasum ; and mild catarrhal inflammation of the intestines. The brain showed degenerative changes, including scattered pyknosis of nerve cells, perivascular edema, and occasional satellitosis.

DISCUSSION

At the beginning, the injury of the adrenal cortex is accompanied by few, if any, clinical symptoms. When these manifestations finally appeared, the adrenals were already extensively damaged.

Neuromuscular and circulatory disturbances can be attributed to adrenal insufficiency[27] as well as to chlorinated hydrocarbon poisoning. Cortisone temporarily alleviated this condition. Whether fhis improvement could be prolonged by repeated cortisone injections and/or appropriate diet and whether regeneration of the damaged cortex could occur with the restriction or suppression of DDD administration have yet to de determined. However, it appears that DDD, in the dosage administered, produces a slow but general toxic effect upon the animal.

In blood examination, the fluctuation, in percentage of eosinophils give a better and more accurate picture of the progress of cortical destruction than do the variations in the number of lymphocytes.

In goats, the degenerative process of the adrenals is generally slow ; it seems to be accelerated, however, in young goats or in those suffering from diseases. Injury to the adrenal cortex starts with necrosis of individual cells or small groups of cells in the

inner zones as early as 6 - 7 days after the beginning of DDD administration. This seems to be in accord with the observation in dogs that the amountt of plasma and urinary 17-hydroxycorticosteroids decreases shortly after initial DDD administration.[8],[5] Simultaneously with damage to the inner zones, a compensatory hypertrophy develops in the outer fasciculata and particularly in the glomerulosa.

The adrenal weight tended to diminish with the progress of the cortical injury. There is evidence of adrenal contraction in the early stages. However, in the late stages of one case, with lymphoid nodule formation and proliferation, the adrenals apparently regain or exceed their original weight and size. Strictly speaking, these changes represent a combination of cortical atrophy and lymphoid metaplasia. Whether a relationship exists between these changes and the adrenal-cortical hypertrophy or hyperplasia observed in the dog by others after administration of some DDD derivatives[15] remains to be determined.

Unlike the above histopathologic picture in goats, the changes of the adrenals in rats limited, occurring primarily in the zona fasciculata and producing no cytologic alteration to the cortical structure.[32] This lack of toxicity has been attributed to a peculiarity of this species.[6],[32]

A comparison of the adrenal cortical changes in goats with those reported in dogs shows similarity with respect to the slow necrotizing and inflammatory phenomena. However, there is a difference in the degree of cortical reduction and in the type of cellular infiltration in dogs.[21] The more marked effect on the adrenals of dogs has been attributed to their greater susceptibility to this toxic agent,[2] since spontaneous cortical atrophy occurred in this animal.[11]

The exact nature of the atrophic process of the adrenal cortex is not known. It has been reported that atrophy produced by DDD in dogs differs from that induced by hormonal means and by starvation.[21] The mode of action of this drug has been attributed to the direct toxic effect on the cortical cells, the sustained high level of this drug in the blood, and the antenergic action of this compound on ACTH.[22],[23],[24] Yet simultaneous administration of ACTH and DDD did not prevent lesions of the adrenal.[18]

It may be that the cytotoxic properties of this compound are

enhanced by the diminishing physiologic activity and, in general, by the aging process of the cells of the inner zones. Since this compound is taken in rapidly by cortical cells[7] and accumulates in high concentration in body fats,[8] the absence of early changes in the glomerulosa may be explained by the fact that lipid accumulation in noticeable amounts in this zone occurs only in later stages and, therefore, that early accumulation of the drug could not be sufficient to produce necrosis. On the other hand, it is possible that deactivation of this enzyme poison to ethylene derivatives by dehydrohalogenation takes place in the glomerular cells in the same way it occurs in the insects which have a resistance to DDT and its analogues and derivatives.[83,84]

The mechanism of this lymphoid metaplasia in goats may be explained by the great potentialities of the free rounded stem or reticular cells of the adrenals. These cells, under certain humoral or environmental conditions brought about by this drug perhaps from the reduction of the corticosteroid output - would produce lymphoblasts, which are comparable, if not identical, in morphology and potentialities to myeloblasts. Thus, instead of cellular elements of the myeloid series (granulocytes), lymphoid cells would be produced from the stem cells and primary lymph nodules with germinal centers would develop. That a specific property of this compound directly or indirectly stimulates lymphoid tissue development is also subtantiated by the presence of lymphatic hyperplasia in all organs and glands in which lymphotic tissue exists.

SUMMARY

Eight goats of various ages were given DDD per os in doses varying from 100 to 280 mg/kg/day over periods ranging from 6 to 65 days. Clinical manifestations of a neuromuscular nature were noted shortly before death in those animals which withstood prolonged treatment. Simultaneously, general enlargement of the lymph nodes, anemia, low sugar level, eosinophilia, and lymphocytosis developed.

During the early stage (one to two weeks) of DDD administration, microscopic examination revealed scattered hemorrhages, cell necrosis, and leukocytic infiltration in the inner cortical zone. With the reduction of this zone, the outer fasciculata and glomerulosa become enlarged with lipid accumulation in the cells.

During the later stages, the above changes increased in intensity and resulted in the disorganization of both inner zones. In addition, a diffuse lymphoid cell infiltration and scattered lymphoid nodules with germinal centers developed in the inner zones extending sometimes to the subcapsular zone. Fibrosis was noticeable. These changes are believed to be due to the specific action of DDD upon the cortical cells.

ACKNOWLEDGEMENT

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TABLE 1

Data concerning goats used, DDD administration, and duration of experiment

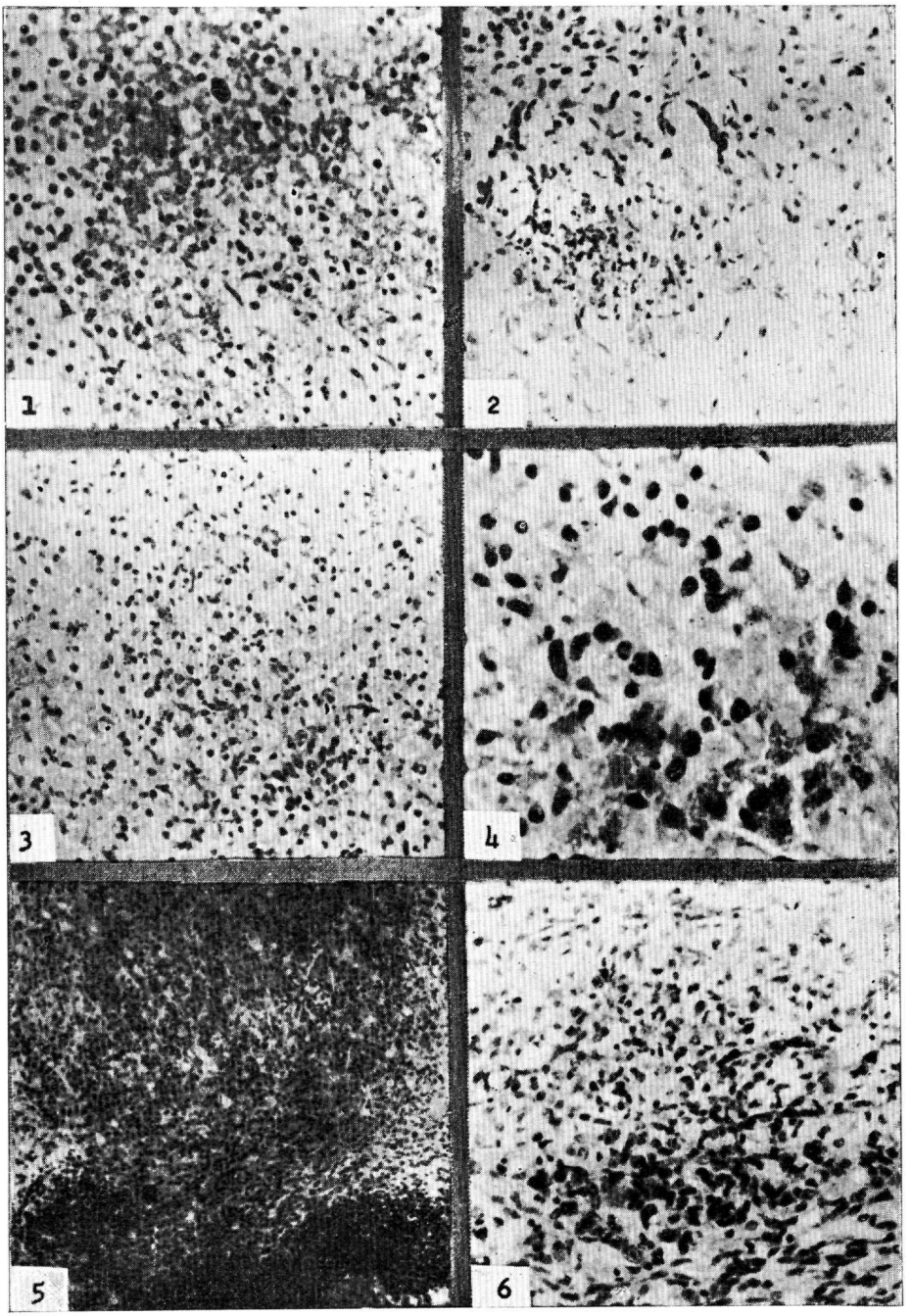
Goat	Age (in mos)	Sex	Initial weight (in lbs.)	Duration of exp. (in days)	Dose per day (in g.)	Total DDD administered (in g.)	Changes in the Adrenals	Remarks
572	3.5		20	6	2.4	14.4	Scattered necrotic foci ; neutrophilic infiltration.	Killed
573	3		20	7	1.2-2.4	14.4	Hemorrhages, scattered pyknosis ; neutrophilic infiltration in the cortex and medulla.	»
576	12		32	7	1.2-2.4	12.0	Fat accumulation Hemorrhages ; other minor changes in the cortex.	»
575	36		38	7	2.4-4.8	31.2	Marked lipid accumulation in the cortical cells.	»
587	3.5		25	20	1.2-2.4	42.0	Shrinkage of the cortex and fatty metaplasia in patches.	»
592	12		38	28	2.4-4.8	88.8	Similar to 587.	Cortisone injected ; died.
544	7		25	28	1.2-2.4	43.5	Advanced destruction.	Died suddenly.
568	10		45	65	1.2-7.2	238.4	Almost complete destruction of the inner cortex ; lymphoid metaplasia.	Moribund ; killed.

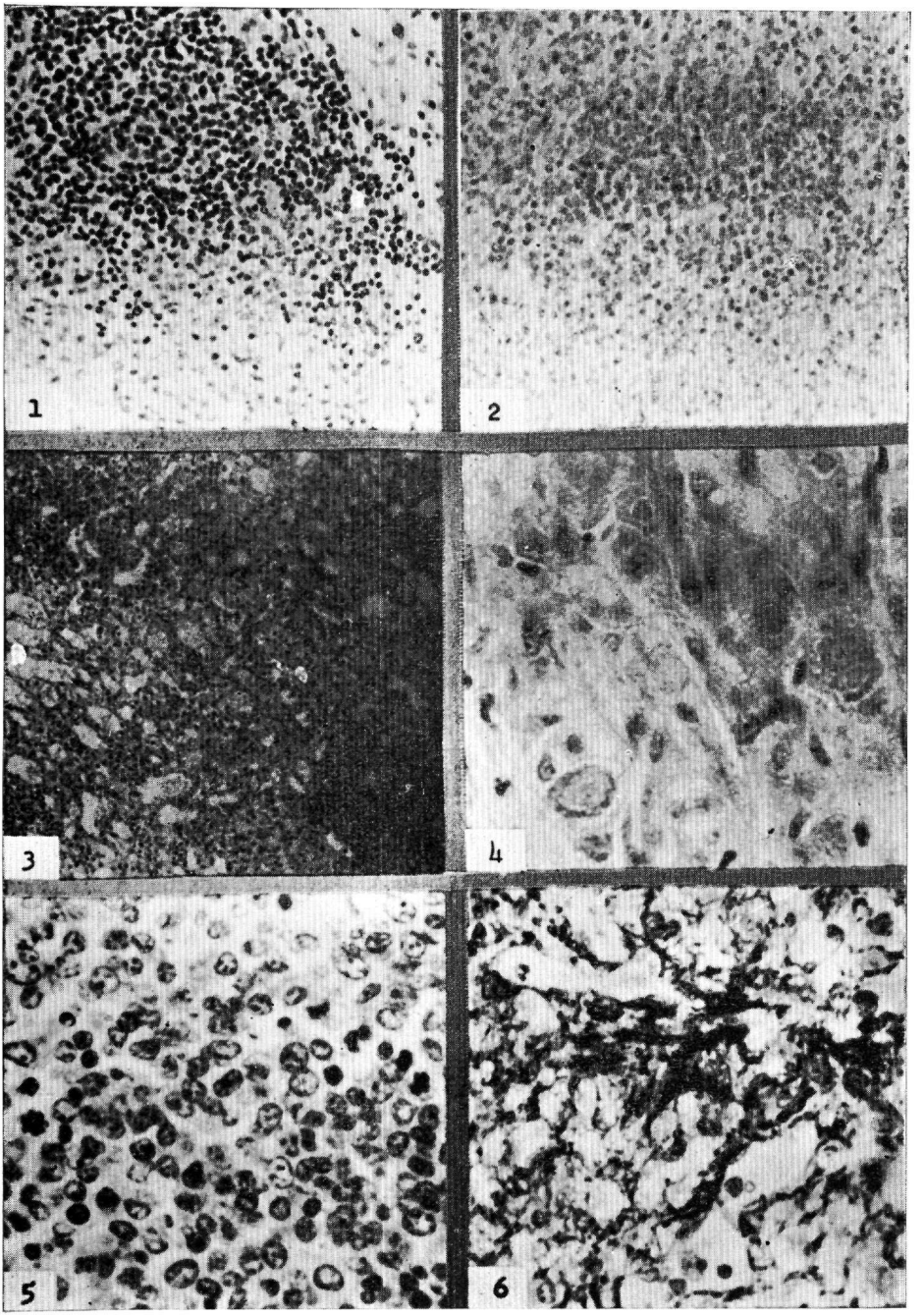
TABLE 2

Weight of adrenals of goats

Goat	Age (in mos.)	Body weight (in lbs.)	Adrenals (in g.) Left - Right		Relative weight of Adrenals (in mg/lb.)	Remarks
587	3.5	25	0.48	0.45	37.2	Group 1: Goats with adrenal lesions; cortical destruction and shrinkage (3 - 9 weeks of DDD administration).
544	7	25	0.98	0.93	76.2	
568	10	45	2.20	2.10	95.5	
592	12	38	0.55	0.45	26.3	
			Average 1.05	0.98	58.8	
572	3.5	20	0.72	0.70	70.0	Group 2: Goats with minor changes of the cortex (6 - 7 days of DDD administration).
573	3	20	0.90	0.70	80.0	
576	12	32	1.30	1.10	75.0	
575	36	38	1.75	1.80	93.4	
			Average 1.17	1.10	79.6	
3210	5	25	0.90	0.80	68.0	Group 3: Control animals.
5860	48	60	2.10	2.00	68.3	
			Average 1.50	1.40	68.2	

PLATE 1

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6

PLATE 1

Fig. 1. A hemorrhagic area in the zona fasciculata of a goat, after six days of DDD administration. H & E stain×125.

Fig. 2. A small necrotic area in the outer fasciculata of a goat, after seven days of DDD administration. Increase of lipid content of the surrounding cells. H & E stain×125.

Fig. 3. Early disorganization in the reticularis of a goat, after eight days of DDD administration. Large necrotic area and increase of lipid content of the cells of the fasciculata. H & E stain×125.

Fig. 4. High power details of area shown in Fig. 3, Plate 1. Nuclear pyknosis and fragmentation, shrunken cytoplasm, and ill defined cellular outlines with slight neutrophil, lymphoid, and undifferentiated cell infiltration. A hemorrhagic spot below. H & E stain×320.

Fig. 5. Narrowed cortex of a goat, after three weeks of DDD administration. Nuclear pyknosis, shrinkage of the cells, and fusion of the fasciculata with the glomerulosa, part of which is pictured here. Diffuse leucocytic infiltration in the outer zone and lymphoid nodules in the zona reticularis along the medullary line. H & E stain x 90.

Fig. 6. Necrotic area in the inner fasciculata of a goat, after four weeks of DDD administration. H & E stain×125.

PLATE 2

Fig. 1. Lymphoid nodule formation in the zona glomerulosa of a goat after nine weeks of DDD administration. H & E stain×125.

Fig. 2. Same adrenal as above. Diffuse lymphocytic infiltration in the zona fasciculata H & E stain×125.

Fig. 3. Same adrenal as above. Complete disorganization of the inner zones; disintegration of the cords; luminal like formation of the sinusoids; marked lymphocytic infiltration; a lymphoid nodule in the reticularis (low-right). H & E stain×90.

Fig. 4. Amyloid bodies in the zona fasciculata of a goat after four weeks of DDD administration. H & E stain×320.

Fig. 5. Lymphoid nodule in the zona fasciculata of a goat, after nine weeks of DDD administration. H & E stain×320.

Fig. 6. Same adrenal as in Fig. 5, Plate 2. Cortical reticulum, (fasciculata). Note disappearance of parenchyma cells; increased collagenous fibers, condensed stroma, and lymphocytic infiltration. Foot's modification of Bielschowsky's stain×320.

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ΠΕΡΙΛΗΨΙΣ

Η ΕΠΙΔΡΑΣΙΣ ΤΟΥ 1,1-ΔΙΧΛΩΡΟ-2,2-ΔΙΣ (ΠΑΡΑΧΛΩΡΟΦΕΝΥΛ-ΑΙΘΑΝΙΟΥ), (DDD ἢ TDE) ΕΠΙ ΤΟΥ ΦΛΟΙΟΥ ΤΩΝ ΕΠΙΝΕΦΡΙΔΙΩΝ ΤΩΝ ΑΙΓΩΝ

Ὑπὸ
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Εἰς ὀκτὼ αἶγας διαφόρων ἡλικιῶν ἐχορηγήθησαν ἀπὸ τοῦ στόματος δόσεις DDD ποικίλλουσαι ἀπὸ 100 μέχρι 280 χιλστγρ. κατὰ χιλιόγραμμον ζῶντος βάρους ἡμερησίως ἐπὶ χρονικὰς περιόδους κυμαινομένας ἀπὸ 6-65 ἡμερῶν. Βραχὺ χρονικὸν διάστημα πρὸ τοῦ θανάνου τῶν ζώων ἐκείνων, εἰς τὰ ὁποῖα ἐγένετο παρατεταμένη χορήγησις τῆς ἀνωτέρω οὐσίας, παρετηρήθησαν ἔκδηλα κλινικὰ συμπτώματα ἀπὸ τοῦ νευρο-μυϊκοῦ συστήματος. Ταὐτοχρόνως παρετηρήθησαν διόγκωσις τῶν λεμφαδένων, ἀναιμία, ὑπογλυχαιμία, ἠωσινοφιλία καὶ λεμφοκυττάρωσις.

Κατὰ τὸ πρώϊμον στάδιον (ἀπὸ 1 μέχρι 2 ἑβδομάδων) τῆς χορηγήσεως τοῦ DDD, ἡ ἱστολογικὴ ἐξέτασις ἀπεκάλυψε διασπάρτους αἱμορραγίας, κυτταρικὴν νέκρωσιν καὶ λευκοκυτταρικὴν διήθησιν τῆς ἔσω στιβάδος τοῦ φλοιοῦ. Ἐκ παραλλήλου πρὸς τὴν μείωσιν τῆς ἀνωτέρω στιβάδος, ἡ δικτυωτὴ ζώνη καὶ ἡ σπειροειδὴς τοιαύτη διογκώθησαν λόγῳ συσσωρεύσεως λιπιδῶν ἐντὸς τῶν κυττάρων.

Κατὰ τὰ μεταγενέστερα στάδια, ἡ ἔντασις τῶν ἀνωτέρω ἀλλοιώσεων ηὐξήθη καὶ εἶχεν ὡς ἀποτέλεσμα τὴν διατάραξιν τῆς ὀργανώσεως ἀμφοτέρων τῶν ἔσω στιβάδων.

Ἐπὶ πλέον διάχυτος διήθησις ὑπὸ λεμφοκυττάρων καὶ διάσπαρτος τοιαύτη ὑπὸ λεμφοζιδίων παρετηρήθη εἰς τὰς ἔσω στιβάδας τοῦ φλοιοῦ, ἐκτεινομένη ἐνίοτε μέχρι τῆς κάψης· ὁμοίως ἦτο ἔκδηλος ἰνώδης ἐξεργασία.

Πιστεύεται ὅτι αἱ ἀνωτέρω ἀλλοιώσεις ὀφείλονται εἰς τὴν εἰδικὴν ἐπίδρασιν τοῦ DDD ἐπὶ τῶν κυττάρων τοῦ φλοιοῦ τῶν ἐπινεφριδίων.