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II. Evaluation of the Toxic Risk of Accumulated DDT in the Rat: During Fat Mobilization

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Abstract. The effects of greatly reduced food intake were investigated in rats which had accumulated three times as much DDT as rats killed with a single dose approaching LD_{50}. DDT and its metabolites mobilized more quickly than the fat deposits. The hypertrophy of the liver due to DDT decreased during food restriction and demonstrated the existence of a large detoxication capacity shown through the high metabolism of the pesticide. The disappearance of *p,p'* DDE was most rapid, followed by *p,p'* DDD then *p,p'* DDT; they did not accumulate in the fat reserves. The half-life of the pesticide, which is normally three months in the rat, was reduced to five days under the experimental conditions. In spite of rapid mobilization, no major toxic signs were detected from either nutritional, physiopathological, or biochemical examinations.

DDT (2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane) accumulates in the fat deposits of the organism and is eliminated very slowly. The biological half-life is about one month in the dog (Deichman *et al.* 1969), two months in the chicken (Lillard and Knoles 1973), three months in the monkey (Durham *et al.* 1963), 26 months in man (Davies *et al.* 1971) and about two months in the rat (Datta and Nelson 1968). Elimination of the pesticide can be accelerated either by mobilization of the lipid stores of the organism or through induction of the detoxication enzyme systems. Studies have been made, for economic and therapeutic reasons, to lower the level of DDT in certain animals and in man. Most of the investigations were based on either low-calorie diets (Kratzer *et al.* 1976), starvation (Deichmann *et al.* 1972, Fitzhugh and Nelson 1947), variable food intake restriction (Donaldson *et al.* 1968, Liska and Stadelman 1969) treatment with enzyme inducers (Alary *et al.* 1971, Davies *et al.* 1971, Lambert and Brodeur 1976a) or finally a combination of the latter two methods (Lambert and Brodeur 1976b). In certain cases, signs of toxicity, some irreversible, were seen to appear simultaneously with lipid mobilization. Fitzhugh and Nelson (1947) observed nervous disorders during starvation in rats which received 600 ppm DDT in their ration. The appearance of toxic signs depends on the dose stocked in the tissues, the physiopathological condition of the animal at the end of

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treatment, the degree to which food intake was restricted, and the detoxication capacity of the organism (Dale *et al.* 1962, Deichmann *et al.* 1972).

This study was undertaken to obtain a better definition of the toxic risk due to a massive mobilization of DDT by measuring, at the same time as the redistribution and elimination of the pesticide, various physiological and biochemical parameters and comparing them to those of animals subjected to the same conditions but not having received the pesticide.

Materials and Methods

Two groups of 16 male OFA strain (Sprague Dawley) rats with an average weight of 164 g were housed in individual cages. The first group (control) received for 52 days, 4 ml/kg body weight intragastrically administered ground-nut oil every morning. The second group (DDT) received 14.5 mg/kg body weight *p-p'* DDT dissolved in the oil (Mitjavila *et al.* 1981). At the end of this period, animals were obtained weighing 308.5 and 306.8 g average, respectively. The DDT group having stocked 23 mg of DDT, an equivalent of three times the dose found in animals killed after acute treatment of DDT.

During the mobilization period animals were starved for three days with access to water; they were then fed for two weeks with 2.5 g food/day/rat. During this period, four rats of the control and treated group were killed at different times (0, 4, 11 and 18 days). These experimental conditions which index the rapid mobilization of DDT, were chosen after a preliminary experiment where smaller number of rats was subjected to several different forms of mobilization by starvation, basing our work on the report by Lambert and Brodeur (1976b). The animals were killed at the different times given above and samples were taken to determine the tissue composition of the various organs using a previously described experimental procedure (Mitjavila *et al.* 1981). Certain enzymes in the brain, liver, and blood were assayed and the level of *p,p'* DDT and it metabolites *p,p'* DDD and *p,p'* DDE were determined. In the study of the mobilization kinetics of DDT and its metabolites, the existence of a possible regression, with time, its linearity and the effect of the duration of food restriction were analyzed. The kinetics in the carcass, the liver, and the brain were compared by the slope comparison test (Schwartz 1963). The results obtained for any toxic effects due to mobilization were subjected to a variance analysis test on a second order factorial plane with four repetitions. This test showed the effects of DDT itself, the effects due to food restriction alone, and any interaction between these two factors, which would show modification of the effect of DDT during mobilization.

Results

Table 1 shows the variations of the level of DDT and its metabolites during food restriction. The carcass contained almost all of the DDT and its metabolites so it can be considered representative of the whole animal. Considering the respective weights (Table 3), the liver and the brain contained a low concentration of DDT, DDD, and DDE. However with respect to the level of total DDT, the liver contained the highest proportion of DDD whereas the carcass and the brain mainly contained DDT. Analysis of these results (Table 1) shows the existence of first order elimination processes between the level of organochloride derivatives and the duration of caloric restriction. For all the equations the absence of a significant variation from the straight line was statistically checked—this confirms the linearity of the semi-log transform. The correlation and the effect of food restriction were always very significant ($P < 0.001$).

The decrease in the level of lipids in the carcass, expressed in grams,

Table 1. Changes in the level of DDT and its metabolites in carcass, liver and brain of rats subjected to food restriction (values expressed in μg)

		Time (days)				Equation parameters[b]	
		0	4	11	18	$a \pm a'$	$b \pm b'$
Carcass	DDE	2068 ± 178.0[a]	910 ± 38.5	301 ± 29.2	88 ± 41.5	−0.0833 ± 0.00839^{c}	3.317 ± 0.0692
	DDD	3178 ± 156.0	1615 ± 34.9	670 ± 16.7	245 ± 13.8	−0.0607 ± 0.00142^{d}	3.482 ± 0.0117
	DDT	17779 ± 1173.0	8834 ± 819.2	4196 ± 341.5	1649 ± 142.4	−0.0556 ± 0.00266^{d}	4.214 ± 0.0219
	Total DDT	23025 ± 1140.0	11359 ± 942.1	5168 ± 328.6	1983 ± 170.2	−0.0576 ± 0.00236^{d}	4.329 ± 0.0195
Liver	DDE	15.9 ± 1.32	7.25 ± 0.341	3.93 ± 0.658	1.86 ± 0.138	−0.0492 ± 0.00362^{d}	1.133 ± 0.0299
	DDD	58.1 ± 4.24	46.5 ± 4.11	28.3 ± 3.23	16.81 ± 2.10	−0.0305 ± 0.00293^{e}	1.772 ± 0.0242
	DDT	57.1 ± 4.31	19.4 ± 2.55	6.32 ± 0.694	3.38 ± 0.897	−0.0689 ± 0.00619^{c}	1.644 ± 0.0511
	Total DDT	131.1 ± 8.17	73.2 ± 3.38	38.6 ± 1.61	22.1 ± 1.87	−0.0423 ± 0.00219^{d}	2.076 ± 0.0181
Brain	DDE	0.98 ± 0.111	0.55 ± 0.056	0.297 ± 0.0219	0.139 ± 0.0118	−0.0454 ± 0.00309^{c}	−0.044 ± 0.0255
	DDD	1.84 ± 0.149	1.00 ± 0.130	0.604 ± 0.0359	0.337 ± 0.0446	−0.0394 ± 0.00361^{c}	0.211 ± 0.0298
	DDT	6.92 ± 0.356	4.30 ± 0.336	2.52 ± 0.215	1.35 ± 0.0146	−0.0386 ± 0.00262^{c}	0.816 ± 0.0216
	Total DDT	9.75 ± 0.349	5.85 ± 0.417	3.42 ± 0.225	1.83 ± 0.152	−0.0393 ± 0.00227^{c}	0.959 ± 0.0187

[a] Mean ± SEM of 4 animals
[b] Equations: $\log y = a(\pm a')x + b(\pm b')$
[c,d,e] Slope comparison in each organ; mean values not sharing a common superscript letter are significantly different ($P < 0.05$)

during caloric restriction (Table 2) also follows a semi-log pattern: the equation is

$$\log y = -0.0296\ (\pm 0.00298) \times +1.598\ (\pm 0.0246)$$

for the controls and $\log y = -0.372\ (\pm 0.00444) \times +1.487\ (\pm 0.0366)$ for the DDT-treated group. In spite of the differences of the slopes, their comparison shows the absence of any significant difference in the rate of lipid mobilization between the control and treated animals. Comparison of the mobilization slopes of the different organochloride derivatives of the carcass (Table 1) with those of the lipids in the treated animals, is always very significant ($P < 0.001$) the organochloride derivatives being mobilized much more rapidly than the lipids. The level of the precursor *p,p′* DDT was seen to drop the slowest, followed by *p,p′* DDD and *p,p′* DDE. The variance analysis test, carried out on the results in Table 3 shows that the proper effect of food restriction is seen through a generalized significant decrease ($P < 0.001$) in the weight of the carcass and the investigated organs except the brain. In fact, the tissue composition of the brain (Table 2) did not vary during food restriction. The interpretation is the same if the results are expressed per gram of brain. However for the

Table 2. Variation of the composition of the carcass brain and liver during food restriction. (values expressed in g)

		Group	Time (days) 0		4		11		18	
Carcass	Proteins	Control	60.9	± 2.11[a]	60.1	± 2.88	49.7	± 0.98	49.5	± 0.54
		DDT	59.8	± 2.59	56.5	± 3.54	48.7	± 2.16	45.3	± 1.77
	Lipids	Control	36.9	± 2.03	34.7	± 3.17	16.2	± 1.25	12.0	± 1.24
		DDT	29.2	± 2.13	22.5	± 2.39	11.6	± 0.68	6.8	± 1.79
	Water	Control	163.4	± 4.77	162.3	± 6.82	134.9	± 2.73	133.4	± 2.18
		DDT	165.1	± 3.37	155.4	± 9.32	135.2	± 4.59	122.6	± 4.98
	Ash	Control	11.28	± 0.585	11.15	± 1.024	10.16	± 0.390	9.90	± 0.344
		DDT	10.10	± 0.777	9.38	± 0.628	7.91	± 0.197	10.33	± 0.954
Brain	Proteins	Control	0.206	± 0.0163	0.200	± 0.0112	0.194	± 0.0153	0.203	± 0.0089
		DDT	0.197	± 0.0166	0.187	± 0.0162	0.189	± 0.0192	0.199	± 0.0053
	Lipids	Control	0.174	± 0.00101	0.149	± 0.0028	0.144	± 0.0102	0.151	± 0.0069
		DDT	0.178	± 0.00114	0.149	± 0.0042	0.145	± 0.0056	0.151	÷ 0.0140
	Water	Control	1.438	± 0.0647	1.435	± 0.0269	1.382	± 0.0533	1.402	± 0.0042
		DDT	1.427	± 0.0377	1.405	± 0.0120	1.399	± 0.0439	1.432	± 0.0148
	Ash	Control	0.0349	± 0.00146	0.0325	± 0.00054	0.0356	± 0.00128	0.0297	± 0.00194
		DDT	0.0385	± 0.00148	0.0378	± 0.00218	0.0381	± 0.00127	0.0309	± 0.00056
Liver	Proteins	Control	2.31	± 0.068	1.81	± 0.113	1.45	± 0.060	1.60	± 0.053
		DDT	2.89	± 0.063	2.26	± 0.220	1.95	± 0.237	1.99	± 0.227
	Lipids	Control	0.462	± 0.0171	0.328	± 0.0217	0.216	± 0.0097	0.213	± 0.0150
		DDT	0.587	± 0.0311	0.434	± 0.0397	0.325	± 0.0122	0.285	± 0.0493
	Water	Control	6.40	± 0.127	5.37	± 0.096	4.81	± 0.096	5.14	± 0.200
		DDT	7.68	± 0.087	6.31	± 0.172	5.66	± 0.166	5.79	± 0.370
	Ash	Control	0.1763	± 0.00472	0.1391	± 0.00339	0.1136	± 0.00592	0.1255	± 0.00286
		DDT	0.2162	± 0.00309	0.1719	± 0.01552	0.1462	± 0.01366	0.1423	± 0.01558
	DNA	Control	0.0241	± 0.00055	0.0232	± 0.00050	0.0226	± 0.00046	0.0223	± 0.00026
		DDT	0.0222	± 0.00057	0.0200	± 0.00052	0.0193	± 0.00044	0.0205	± 0.00034

[a] Mean ± SEM of 4 animals

Table 3. Changes in the weight of various organs (g) during food restriction

	Group	Time (days) 0	4	11	18	Proper effect of DDT F^1_{24}	Effect of food restriction F^3_{24}	Interaction F^3_{24}
Live weight	Control	308.5 ± 6.18[a]	292.2 ± 9.69	239.1 ± 4.91	238.2 ± 17.68	2.66	19	<1
	DDT	306.8 ± 6.68	262.2 ± 27.38	232.5 ± 7.77	221.5 ± 34.37		***	
Carcass	Control	268.2 ± 6.15	261.5 ± 8.29	211.3 ± 3.8	206.5 ± 4.23	5.6	42	<1
	DDT	265.2 ± 5.64	243.7 ± 13.38	203.8 ± 6.70	184.8 ± 7.44	*	***	
Liver	Control	9.36 ± 0.179	7.64 ± 0.115	6.56 ± 0.135	7.09 ± 0.199	44	35	<1
	DDT	11.36 ± 0.117	9.16 ± 0.422	8.08 ± 0.375	8.20 ± 0.649	***	***	
Brain	Control	1.836 ± 0.0227	1.836 ± 0.0346	1.795 ± 0.0640	1.844 ± 0.0173	<1	<1	<1
	DDT	1.822 ± 0.0447	1.811 ± 0.0141	1.788 ± 0.0547	1.841 ± 0.0173			
Heart	Control	0.839 ± 0.0109	0.735 ± 0.0173	0.688 ± 0.0032	0.656 ± 0.0158	1.8	15.2	<1
	DDT	0.836 ± 0.0378	0.690 ± 0.0557	0.679 ± 0.0448	0.590 ± 0.0363		***	
Spleen	Control	0.643 ± 0.0286	0.572 ± 0.0420	0.455 ± 0.0100	0.483 ± 0.0281	8.4	13.3	1.6
	DDT	0.733 ± 0.0306	0.567 ± 0.0192	0.507 ± 0.0479	0.620 ± 0.0420	**	***	
Kidney	Control	2.041 ± 0.0281	1.829 ± 0.0755	1.671 ± 0.0441	1.647 ± 0.0209	<1	20	<1
	DDT	2.113 ± 0.0461	1.785 ± 0.1444	1.614 ± 0.0441	1.562 ± 0.0565		***	
Testicles	Control	2.900 ± 0.0259	2.776 ± 0.0563	2.730 ± 0.1087	2.712 ± 0.0589	<1	5.4	<1
	DDT	3.059 ± 0.0472	2.905 ± 0.0974	2.690 ± 0.0880	2.645 ± 0.1301		**	

[a] Mean ± SEM of 4 animals. * $P < 0.05$: ** $P < 0.01$; *** $P < 0.001$

carcass, food restriction caused a very significant decrease ($P < 0.001$) of all tissue constituents with the exception of the level of ash (Table 2). The same is true when the results are expressed per gram fresh weight. Food restriction had the same effect on the constituents of the liver which all decreased significantly ($P < 0.001$) (Table 2). Yet when the results are expressed per gram fresh weight only the concentration of water ($P < 0.01$) and DNA ($P < 0.001$) increased significantly whereas that of the lipids was seen to drop sharply ($P < 0.001$).

During the period of partial starvation, in spite of the withdrawal of DDT administration, the effects of the pesticide continued to be seen, mainly through a very large decrease of the lipids in the carcass ($P < 0.001$) (Table 2), which partly explains the differences in carcass weight ($P < 0.05$) (Table 3). No effect of DDT was seen on the brain either on the weight or the tissue composition. However, in animals which received DDT the weight of the spleen and the liver (Table 3) as well as the levels of lipids, protein, ash and water of the latter were always greater ($P < 0.001$) (Table 2) than the controls. The level of DNA in the liver was significantly lower in the treated animals ($P < 0.001$) so the ratio protein/DNA, although significantly decreased ($P < 0.001$) under the effect of caloric restriction, was always higher under the effect of DDT.

Figure 1 shows an increase in the haemocrit value during the 3-day starvation period in both groups of animals—probably due to haemoconcentration. Subsequently, the values returned to normal. A progressive decrease was noted in lipemia during food restriction, but in the DDT-treated rats it remained slightly higher. The level of plasma proteins increased for both groups of animals with a maximum on the 11th day of food restriction.

Variance analysis showed a significant proper effect ($P < 0.001$) of partial starvation on the enzyme activities (Table 4). The activity of the plasmatic enzymes and hepatic cholinesterase increased whereas the total ATPase activity of the liver was significantly decreased ($P < 0.001$). In the brain the ATPase activity rose slightly and that of cholinesterase fell significantly ($P < 0.001$). No significant interaction was noted between the proper effects of DDT and those of caloric restriction.

Discussion

The results confirm that DDT, accumulated in the lipids of the organism, can be mobilized and eliminated during severe food restriction. The half-life of DDT has been evaluated at about two months in the rat (Datta and Nelson 1968). Under our experimental conditions and using the equations presented in Table 1, half-life of total DDT was five days. This confirms the high degree of mobilization of DDT through food restriction. Dale *et al.* (1962) reducing the food intake by 50% for 10 days, and Deichmann *et al.* (1972) starving the animals for six days observed an increase in the levels of DDT and its metabolites in the fatty tissue. With respect to the results of Dale *et al.* the difference was probably due to the method used for adipose tissue sampling. In effect, in order to account for the selective resistance to starvation of the various organs (Cahill 1970, Rumsey *et al.* 1967), we extracted the totality of the lipids, since the possibility could not be dismissed that first, part of the DDT mobilized in the peripheral tissues would become redistributed in the less easily mobilized fats (Lambert and Brodeur 1976b). The difference with the results of Deichmann is

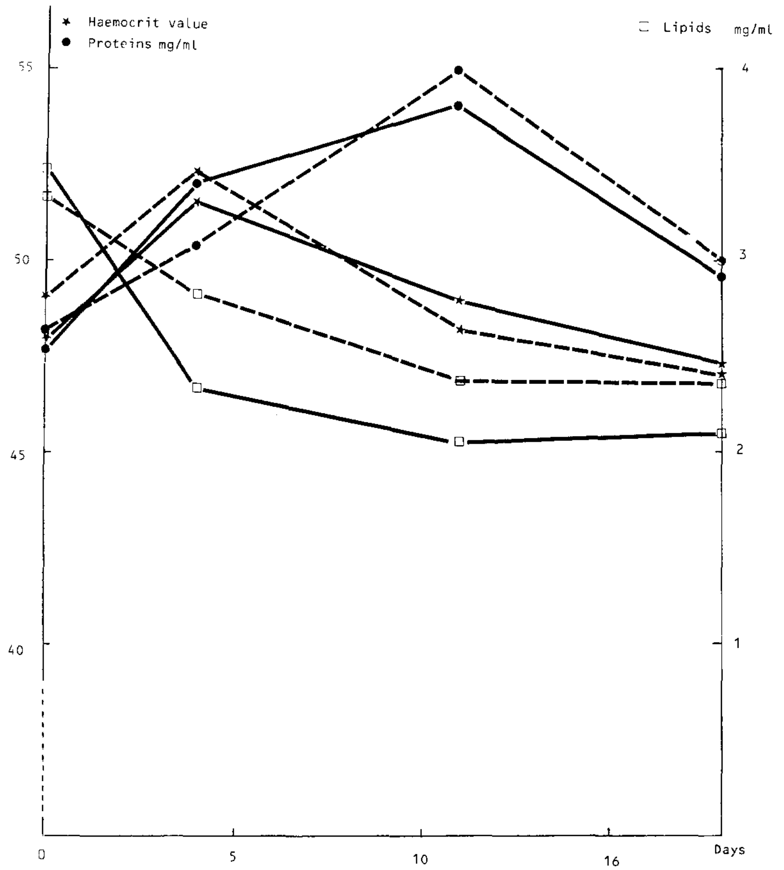

Fig. 1. Changes in the level of plasmatic lipids, proteins and haemocrit value during food restriction in control (——) and DDT treated animals (----)

probably due to the fact that starvation was much more severe and the period of observation much shorter than in our experimental conditions. In the present investigation, the rate of mobilization of DDT and its metabolites in the carcass was significantly faster than that of the lipids. So DDT can not become concentrated in the total lipids of the organism. The relatively high quantities of DDD with respect to DDT in the liver can be explained by the fact that this organ is the site of metabolism of DDT to DDD (Alary *et al.* 1971, Lambert and Brodeur 1976a, Peterson and Robison 1964, Radomski *et al.* 1968). The total quantity of DDT mobilized was three times greater than that found in animals killed with a dose of 200 mg of DDT (Mitjavila *et al.* 1981). Nevertheless, no important physiopathological signs were seen in treated animals when compared to the controls.

Although the first symptoms of DDT toxicity are through the nervous system (Hayes 1959, Woolley 1976), no significant differences were seen in the animals either in the composition of the brain or in the activity of the studied enzymes. Yet, ATPase is normally inhibited during DDT poisoning (Akera *et al.* 1971, Matsumura *et al.* 1969, Witherspoon and Wells 1975) as is the case for

Table 4. Changes in various enzyme activities in control and in DDT treated animals during food restriction

Enzyme	Organs	Group	Time (days) 0	4	11	18
Cholinesterase	Plasma U/L	Control	355.5 ± 10.80[a]	400.0 ± 2.19	395.2 ± 8.84	413.0 ± 14.26
		DDT	350.0 ± 5.67	407.5 ± 10.88	400.0 ± 13.28	404.3 ± 10.24
	Liver U/g	Control	1.74 ± 0.034	1.67 ± 0.064	1.70 ± 0.102	2.27 ± 0.144
		DDT	1.79 ± 0.160	1.72 ± 0.096	1.98 ± 0.115	2.13 ± 0.133
	Brain U/g	Control	10.67 ± 0.282	10.71 ± 0.559	9.16 ± 0.355	8.84 ± 0.278
		DDT	10.48 ± 1.044	10.15 ± 0.325	7.13 ± 0.699	6.17 ± 0.242
Total ATPase	Brain (mM Pi/h/g)	Control	2.01 ± 0.143	2.06 ± 0.143	2.34 ± 0.121	2.53 ± 0.045
		DDT	1.98 ± 0.103	2.16 ± 0.161	2.51 ± 0.208	2.52 ± 0.088
	Liver (mM Pi/h/g)	Control	1.46 ± 0.046	1.00 ± 0.065	1.38 ± 0.336	1.33 ± 0.057
		DDT	1.27 ± 0.075	0.88 ± 0.083	1.16 ± 0.018	0.96 ± 0.124
Alkaline phosphatase	Plasma U/L	Control	31.7 ± 0.735	34.7 ± 0.256	34.4 ± 0.770	35.4 ± 1.288
		DDT	32.7 ± 0.695	33.7 ± 1.161	35.4 ± 0.962	35.5 ± 0.771
GOT	Plasma U/L	Control	31.2 ± 1.10	51.9 ± 3.66	80.0 ± 2.55	53.0 ± 3.39
		DDT	34.7 ± 2.13	49.7 ± 1.93	59.5 ± 4.77	44.9 ± 1.89
GPT	Plasma U/L	Control	9.12 ± 1.048	11.97 ± 0.963	10.87 ± 0.826	12.80 ± 1.442
		DDT	11.12 ± 0.965	12.12 ± 0.826	12.87 ± 0.825	13.62 ± 0.427

[a] Mean ± SEM of 4 animals

cholinesterase (Narahashi 1971). This is explained by the fact that in the brain, where DDT is not metabolized and where the lipids are essentially composed of structural phospholipids, which are not mobilized, a progressive decrease is seen in the concentration of this pesticide. This organ presents the real distribution and excretion kinetics of DDT and its metabolites.

Insofar as the effects of DDT on the weights of the different organs are concerned, Fitzhugh and Nelson (1947) have already shown a slight increase in the weight of the spleen under the action of DDT. The difference between control and treated animals decreases as the DDT becomes mobilized. The weight decrease of the carcass, under the effect of DDT, is mainly due to a decrease in the level of lipids in the treated animals, this has been demonstrated by Deichmann *et al.* (1972) and Radomski *et al.* (1968). The difference in the level of lipids in the carcass was significant at the end of the period of treatment and did not become greater during restriction. So DDT mobilization did not accentuate lipid mobilization in the treated animals and, furthermore, comparison of the total lipid mobilization slopes between the controls and the treated animals is not significant. Only the weight of the liver was appreciably higher in the controls all through partial starvation with a progressive attenuation as the DDT was mobilized. In particular, examination of the liver tissue composition showed that when the results were expressed as a concentration only, the level of lipids in the liver was seen to be slightly higher—this could be a consequence of DDT poisoning (Anonymous 1966). However the hypertrophy observed during poisoning decreased during the period of caloric restriction at the same time as DDT, which is a powerful enzyme inducer in the rat (McLean and McLean 1966), was eliminated. The ratio protein/DNA in the controls moved from 96 at the start of starvation to 72 at the end of caloric restriction whereas it went from 131 to 97 in the treated animals. It would seem, therefore, that the physiopathological state of the animals treated with DDT was approximately the same as that of the controls at the end of food restriction. The capacity of adaptation of the enzyme system in the liver seems to be sufficient to metabolize DDT as it is mobilized and prevent an increase in the level of blood DDT which could induce sign of toxicity, particularly in the central nervous system. From these results, it would seem improbable that the levels of DDT residues in the human body constitute a real danger in the case of mobilization. The present results do not in fact give any information on the carcinogenic effect of DDT which was demonstrated in the monkey (Durham *et al.* 1963) but which is very debatable in man (Radomski *et al.* 1968) and in the rat (Radomski *et al.* 1965). Similarly, any possible mutagenic effects which can be more or less attributed to DDT in the rat (Palmer *et al.* 1973) as well as its teratogenic properties (Smith *et al.* 1970) were not considered. It is, however, interesting to compare the levels of DDT in the environment with the doses administered and mobilized in this experiment and the physiopathological condition of the animals. Deichmann (1970) has already raised the problem posed by the replacement of DDT—which has known and sometimes over-evaluated effects—with pesticides having toxic properties which are often much less known.

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