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LIVER NECROSIS FROM PARACETAMOL

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Paracetamol was originally used therapeutically in the latter nineteenth century but did not receive much attention until after the 1940s when it was found to be a metabolite of phenacetin (Smith, 1958). It was given the approved name "Paracetamol" by the British Pharmacopoeia Commission in February, 1957, and was introduced into the 1963 edition of the British Pharmacopoeia. It has been considered as a possible substitute for phenacetin (e.g., Cornely & Ritter, 1956) following reports of interstitial nephritis allegedly due to phenacetin (e.g., Editorial, 1965). We decided to study the toxicity of paracetamol following previous work in this laboratory on the acute oral toxicity of phenacetin (Boyd, 1959 and 1960). The most interesting finding was that when death was delayed there was an associated necrosis of the liver.

The initial objective was to compare the acute toxicity of paracetamol with that of phenacetin. Therefore the project was designed so that toxicity would be determined at the range of the LD50 given to albino rats by intragastric cannula. The oral LD50 of paracetamol has been reported somewhat lower than that of phenacetin in mice and higher in rats (Smith, 1958). In rats it has been found of the order of 3.0 to 4.5 g/kg (Renault, Rohrbach & Dugniolle, 1956 ; Smith, 1958).

METHODS

The experiments were performed upon young male CBL-Wistar albino rats of 100 to 200 g body weight fed Purina laboratory chow and water *ad libitum*. Sixteen hours before paracetamol administration each rat was placed in a metabolism cage, 1 rat per cage, and deprived of food but not water. Paracetamol (Eastman) was then administered by intragastric cannula as a freshly prepared suspension in distilled water. The suspension was stabilized by the addition of gum tragacanth powder to 0.2% (w/v) and the volume administered was maintained constant at 20.0 ml./kg since Ferguson (1962) has shown that drug toxicity can increase with increasing volume per kg of distilled water vehicle. Each of the following doses, expressed as g/kg, was given to 15 to 20 rats: 0.0, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 6.0, and 7.0. Following drug administration the rat was returned to its metabolism cage which contained a weighed amount of food (50 g) and a measured amount of water (100 ml.).

Clinical measurements were made upon each rat at daily, or shorter if indicated, intervals for 5 days. Survivors were then returned to the animal boarding quarters and observed for one month. Clinical measurements included body weight in g, food consumption in g rat feed/kg body weight per 24 hr, water consumption in ml./kg per 24 hr, colonic temperature in ° C, urinary volume in ml./kg per 24 hr, urinary glucose output in mg/kg per 24 hr, urinary *p*H of 24 hour sample, urinary protein output in mg/kg per 24 hr, and other clinical signs quantitated at 1+ to 4+. Colonic temperature was recorded by a Thermistemp Telethermometer (Yellow Springs Instrument

Company, Inc., Yellow Springs, Ohio). Urinary glucose, protein and *p*H were measured with Ames Combistix Reagent Strips.

Gross pathology was noted at autopsy on all animals which died. The fresh wet weight and water level of organs listed in Tables 5 and 6 below were determined upon 10 rats which died at 4 to 6 hr, and which could be autopsied within 1 hour of death to avoid postmortal changes reported by Boyd & Knight (1963), and upon 10 controls. Weights and water levels were also measured upon 10 rats which survived doses in the range of the LD50 at 24 hr and upon 13 rats at 1 month with 20 and 8 controls at these respective intervals. Weight was measured to 0.1 mg on a Gram-atic Semi Micro Balance. The sample of muscle (Tables 5 and 6) was the left half of the ventral abdominal wall muscle layer. The contents of the gastrointestinal tract were removed by a standardized technique of washing and milking before each weighing. Water levels were measured upon the various organs (see Table 6) by drying a weighed aliquot to constant weight at 95° C in a Fisher Forced Draft Isotemp Oven. The aliquot of skin used for water analysis was from the dorsolumbar region. After removing the various organs listed in Table 6, the residual carcass was weighed, cut into small pieces, homogenized in a Waring Blendor, and an aliquot weighed for water analysis. Water levels were calculated as g/100 dry weight of tissue. Histopathologic examinations were made upon blocks of tissue fixed in Lillie's Buffered Formalin and sections were stained by haematoxylin-phloxine-saffron. Statistical methods were those of Croxton (1953).

RESULTS

The LD50 $\pm$ S.E. of paracetamol was found to be 3.71 $\pm$ 0.83 g/kg body weight. An estimate of the maximal LD0 $\pm$ S.E. was calculated as 0.9 $\pm$ 0.8 g/kg and of the minimal LD100 6.5 $\pm$ 0.8 g/kg.

The interval to death varied inversely with dosage as illustrated in Fig. 1. The large standard error in Fig. 1 indicates that there was a considerable range even in the mean interval and in each mean there was a further wide range of individual values. At doses less than the LD50 half the deaths occurred at over 24 hr, and at doses greater than the

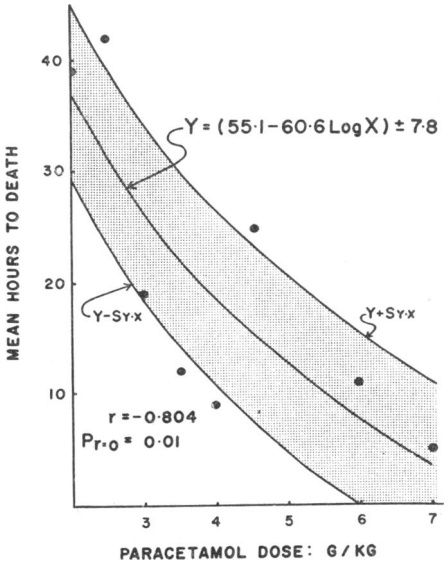

Fig. 1. The regression on dose of paracetamol of mean hr to death

LD50 three-quarters of the deaths occurred within the first 12 hr. At the LD50, the mean interval to death was 21 hr.

The immediate signs of toxicity within 5 hr of administration of paracetamol have been summarized in Table 1. The animals became listless, hypokinetic and responded less to stimuli such as prodding, noise or blowing against the grain of the fur. The tail tended to be extended in a Straub-like reaction, some tremor appeared, and there was a mild degree of pallor of the lips, eyes and paws. The intensity of listlessness, decreased response to stimuli, and of tremor was dose-dependent as exemplified in Fig. 2.

Clinical signs at 24 hr after drug administration are summarized in Tables 2 and 3 and control measurements in Table 4. Clinical signs included loss of body weight, a

TABLE 1

CLINICAL SIGNS DURING 5 HR FOLLOWING ADMINISTRATION OF PARACETAMOL IN THE RANGE OF THE ORAL MEDIAN LETHAL DOSE

The clinical signs were assessed as 1+ to 4+ and are expressed as mean ± S.D. difference from controls, specifically as $\bar{X}(\bar{X}d-\bar{X}c)$ where $\bar{X}d$ is the mean in each drug-treated group and $\bar{X}c$ the mean of the controls. $\bar{X}d$ was greater than $\bar{X}c$ at $P<0{\cdot}05$ in all instances except where the mean difference equalled zero. N refers to the number of animals observed

	Hours after paracetamol			
Clinical sign	0·5 N = 119	1 N = 119	3 N = 106	5 N = 95
Listlessness	2·8±0·6	3·6±0·3	3·7±0·6	3·7±0·2
Decreased response to stimuli	3·4±0·5	3·5±0·4	3·8±0·3	3·5±0·5
Tail extension	0·0±0·0	1·4±0·7	1·6±1·0	0·7±0·4
Tremor	0·0±0·0	0·9±0·6	1·2±0·9	1·2±0·4
Pallor	0·0±0·0	0·1±0·05	0·2±0·1	0·0±0·0

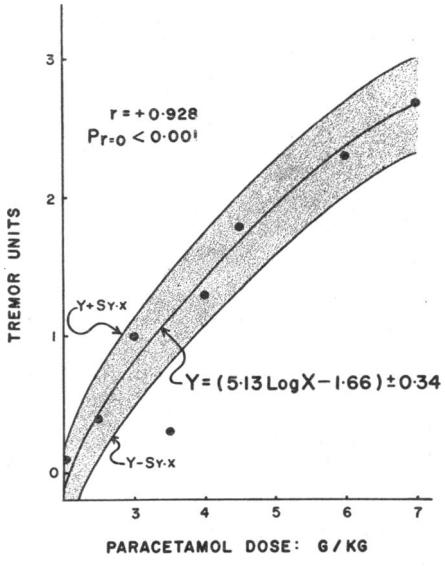

Fig. 2. The regression on dose of paracetamol of mean clinical units of tremor measured 3 hr after drug administration.

decrease in food and water intake, hypothermia and aciduria, listlessness, decreased response to stimuli, tremor, tail extension and pallor.

The premortal signs were marked hypothermia and stupor, accompanied by pallor, tremor, tail extension, anuria, no food and water intake, and marked loss of body weight. A few animals had a dacryorrhea. The immediate cause of death was respiratory failure. In six rats, death was delayed to the second to seventh days and they exhibited, in addition, ataxia, a dry skin, erection of the penis and occult blood in the urine.

On gross observation at autopsy, the cardiac and pyloric stomach, small bowel, thymus gland and brain appeared inflamed. The kidneys and spleen were pale. The liver and kidneys were spotted and the submaxillary salivary glands had a watery consistency.

A summary of the changes in fresh wet weight of body organs at autopsy is presented in Table 5. At 4 to 6 hr there had occurred a significant loss of weight in small bowel and spleen, and a significant gain in salivary glands. At 24 hr significant loss of weight

TABLE 2

CLINICAL MEASUREMENTS MADE AT DAILY INTERVALS AFTER ADMINISTRATION OF PARACETAMOL IN THE RANGE OF THE ORAL MEDIAN LETHAL DOSE

The results are expressed as the mean ± standard error per cent change from the day before drug administration except those for urinary glucose which are expressed as the mean ± standard error difference from the day before drug

Group	No.	Days after drug administration 1	2	3	4
Body weight (g)					
Controls	20	+9·2±2·4	+12·3±2·5	+16·8±2·4	+21·5±2·3
Survivors	58	−1·0±2·2	− 0·2±7·1	+ 3·2±0·9	+ 6·3±1·5
Non-survivors	19	−6·7±5·1	−12·6±2·9	−16·7±1·4	
Food intake (g/kg body weight per 24 hr)					
Controls	20	+ 3·3±6·5	− 4·2±8·4	+ 6·6±5·8	− 6·6±4·1
Survivors	58	−51·0±8·3	−50·0±7·7	−22·2±6·3	−10·7±6·4
Non-survivors	19	−95·2±4·1	−97·0±3·0	−97·0±2·1	
Water intake (ml./kg body weight per 24 hr)					
Controls	20	+21·6± 7·2	−10·7±8·0	− 5·1± 3·0	− 6·3±6·9
Survivors	58	−69·0± 6·3	−53·6±7·0	−22·9± 6·8	−11·6±6·2
Non-survivors	19	−90·0±10·0	−91·6±8·0	−80·2±20·1	
Colonic temperature (° C)					
Controls	20	− 0·2±0·2	0·0±0·2	0·0±0·3	0·0±0·1
Survivors	58	− 2·9±1·2	−0·9±0·7	−0·1±0·2	+0·1±0·2
Non-survivors	19	−10·5±1·5	−6·5±2·0	−9·0±1·0	
Urinary volume (ml./kg body weight per 24 hr)					
Controls	20	−11·8±22·8	− 27·0±21·3	+ 5·9± 40·0	+17·6±16·2
Survivors	58	−12·7±22·7	+ 11·2±42·2	+100·1± 39·3	+92·9±30·0
Non-survivors	19	−34·2±36·0	+108·1±40·2	+535·0±310·1	
Urinary protein (mg/kg body weight per 24 hr)					
Controls	20	−59·0±55·7	−26·2±75·1	+51·4±77·4	+33·5±85·4
Survivors	58	+31·1±42·5	+52·0±28·5	+18·6±33·0	+ 3·9±35·0
Non-survivors	19	+14·3±12·2	−17·7±29·2	−13·3±41·2	
Urinary pH (24-hr sample)					
Controls	20	−2·9±2·9	+ 2·9± 4·2	+ 2·9± 3·1	−5·8±3·0
Survivors	58	−9·1±1·8	− 6·1± 2·0	− 0·4± 2·9	+6·2±3·1
Non-survivors	19	−9·3±1·2	+15·1±14·0	+20·0±18·2	
Urinary glucose (mg/kg body weight per 24 hr)					
Controls	20	0·0±0·0	0·0±0·0	0·0±0·0	0·0±0·0
Survivors	58	0·0±0·0	0·0±0·0	+0·6±0·8	0·0±0·0
Non-survivors	19	0·0±0·0	0·0±0·0	0·0±0·0	

TABLE 3

CLINICAL SIGNS RECORDED DURING 3 DAYS FOLLOWING ADMINISTRATION OF PARACETAMOL IN THE RANGE OF THE ORAL MEDIAN LETHAL DOSE

The signs were quantitated as 1+ to 4+ and are expressed as mean ± standard error. None of these signs was present on the day before drug administration nor in the controls given water only

Group	No.	Days after drug administration 1	2	3
Listlessness				
Survivors	58	1·2±0·4	0·4±0·2	0·0±0·0
Non-survivors	19	3·8±0·1	3·5±0·5	4·0±0·5
Decrease in response to stimuli				
Survivors	58	0·9±0·3	0·0±0·0	0·0±0·0
Non-survivors	19	3·6±0·2	1·0±0·3	1·0±0·2
Tremor				
Survivors	58	0·1±0·1	0·0±0·0	0·0±0·0
Non-survivors	19	1·2±0·3	1·0±0·2	1·0±0·4
Tail extension				
Survivors	58	0·1±0·1	0·0±0·0	0·0±0·0
Non-survivors	19	1·7±0·3	1·8±0·4	1·8±0·4
Pallor				
Survivors	58	0·1±0·1	0·0±0·0	0·0±0·0
Non-survivors	19	0·9±0·3	0·8±0·2	0·8±0·2

TABLE 4

A SUMMARY OF CLINICAL MEASUREMENTS MADE BEFORE DRUG ADMINISTRATION

Measurement	Units	Mean ± S.D.
Body weight	g	154 ±22
Food intake	g/kg per 24 hr	120 ±34
Water intake	ml./kg per 24 hr	158 ±41
Colonic temperature	°C	36·5± 0·2
Urinary volume	ml./kg per 24 hr	8·5± 9·8
Urinary protein output	mg/kg per 24 hr	3·9± 3·2
Urinary glucose output	mg/kg per 24 hr	0·0± 0·0
Urinary *p*H		6·9± 0·9

had occurred in all organs except the adrenal glands, brain, cardiac stomach, lungs, salivary glands, and testes.

Changes in organ water levels are listed in Table 6. At 4 to 6 hr there were significant increases in water content in kidneys and salivary glands and decreases in brain, colon, muscle, and testes. At 24 hr changes were mixed, the greatest increases being in small bowel and salivary glands and the most evident decrease in the thyroid gland.

A summary of the histopathologic findings at autopsy is presented in Table 7. When death occurred in less than 24 hr, the main finding was capillary-venous congestion of most organs. In addition there occurred renal tubular oedema, hepatic centrilobular pale-staining, oedema and hypogranulation of the submaxillary serous glands and contracted red pulp in the spleen.

When death occurred at 1 to 7 days, the main finding was hepatic necrosis associated with degenerative changes in the brain, kidneys, serous salivary glands, thymus and thyroid glands and the tunica media of the arterioles, and an occasional gastric ulcer. The earliest evidence of hepatic necrosis was centrilobular sinusoidal congestion and

TABLE 5

THE EFFECT OF ADMINISTRATION OF PARACETAMOL IN THE RANGE OF THE ORAL MEDIAN LETHAL DOSE ON THE FRESH WET WEIGHT OF BODY ORGANS

The results are expressed as mean % change from controls with, in parentheses, the probability (*P*) that the mean % change was zero

	Interval after drug administration		
Organ	4 to 6 hr (N = 10 drug + 10 control)	24 hr (N = 10 drug + 20 control)	1 month (N = 13 drug + 8 control)
Adrenal glands	+ 2·2 (0·9)	+ 8·8 (0·1)	+ 2·1 (0·6)
Brain	+ 1·9 (0·9)	− 1·8 (0·3)	+ 2·4 (0·5)
Gastrointestinal tract:			
Cardiac stomach	+ 4·1 (0·7)	− 2·5 (0·6)	+ 0·2 (0·9)
Pyloric stomach	+ 2·4 (0·8)	−12·5 (<0·001)	− 6·3 (0·4)
Small bowel	−13·3 (0·05)	−15·0 (0·005)	− 2·7 (0·7)
Cecum	−14·2 (0·1)	−20·6 (0·02)	+ 8·0 (0·1)
Colon	+ 3·2 (0·7)	−11·1 (0·05)	+ 8·5 (0·1)
Heart	− 4·6 (0·1)	− 9·5 (0·005)	+ 1·2 (0·9)
Kidneys	+ 3·5 (0·8)	− 6·5 (0·02)	+ 6·0 (0·2)
Liver	− 7·7 (0·1)	−27·3 (<0·001)	− 1·6 (0·7)
Lungs	+ 3·4 (0·6)	+ 0·5 (0·9)	− 1·4 (0·9)
Muscle (ant. abd. wall)	+ 5·3 (0·5)	−18·3 (<0·001)	+ 5·5 (0·5)
Salivary glands (submax.)	+32·3 (0·05)	− 0·3 (0·9)	+ 8·7 (0·7)
Skin	+ 3·3 (0·5)	−15·6 (<0·001)	+ 8·8 (0·3)
Spleen	−26·7 (0·02)	−21·5 (0·05)	0·0 (1·0)
Testes	+ 3·6 (0·8)	+ 4·4 (0·8)	− 5·3 (0·3)
Thymus gland	−11·0 (0·1)	−49·8 (<0·001)	−13·3 (0·02)
Thyroid gland		− 9·8 (0·05)	
Residual carcass	+ 5·3 (0·2)	− 9·1 (<0·001)	+ 3.4 (0·6)

TABLE 6

THE EFFECT OF ADMINISTRATION OF PARACETAMOL IN THE RANGE OF THE ORAL MEDIAN LETHAL DOSE ON THE WATER LEVEL, MEASURED AS G PER 100 G DRY WEIGHT, OF BODY ORGANS

The results are expressed as mean % change from controls with, in parentheses, the probability (*P*) that the mean % change was zero)

	Interval after drug administration		
Organ	4 to 6 hr	24 hr	1 month
Adrenal glands	+ 2·8 (0·8)	+ 4·4 (0·5)	+ 1·2 (0·7)
Brain	− 4·4 (0·05)	− 0·5 (0·6)	− 6·8 (0·2)
Gastrointestinal tract:			
Cardiac stomach	+ 1·7 (0·8)	− 7·0 (0·05)	−16·8 (0·01)
Pyloric stomach	− 2·2 (0·7)	− 3·8 (0·05)	+ 2·7 (0·7)
Small bowel	− 2·4 (0·7)	+12·2 (0·005)	+ 6·3 (0·2)
Cecum	− 5·1 (0·5)	+ 0·2 (0·9)	− 3·5 (0·5)
Colon	−16·5 (0·001)	− 3·1 (0·5)	+ 8·6 (0·2)
Heart	+ 0·8 (0·9)	− 5·0 (0·005)	+ 1·5 (0·8)
Kidneys	+18·7 (0·001)	− 0·6 (0·8)	+ 1·2 (0·9)
Liver	0·0 (1·0)	+ 5·1 (0·05)	− 0·8 (0·9)
Lungs	+ 4·8 (0·1)	− 5·6 (0·01)	− 4·5 (0·1)
Muscle (ant. abd. wall)	−11·3 (0·05)	+ 3·1 (0·5)	− 3·4 (0·5)
Salivary glands (submax.)	+21·2 (0·001)	+15·7 (0·01)	+ 0·4 (1·0)
Skin	− 3·4 (0·7)	+ 2·9 (0·6)	− 3·1 (0·7)
Spleen	− 4·6 (0·3)	− 6·4 (<0·001)	+ 1·6 (0·9)
Testes	− 7·0 (0·001)	− 4·4 (0·01)	− 0·3 (1·0)
Thymus gland	− 2·6 (0·8)	− 5·4 (0·1)	+ 0·9 (0·9)
Thyroid gland		−48·8 (<0·001)	
Residual carcass	+ 3·9 (0·6)	+ 0·3 (0·3)	−11·8 (0·001)

pale-staining which appeared at 1 to 1½ days. As the condition progressed, the sinusoidal wall appeared to weaken and red blood cells could be found scattered throughout the parietal cells or in microscopic haemorrhagic areas. The parietal cells then showed pyknosis and degnerative changes and as the nucleus disappeared they became swollen ghost cells. In other areas, the anuclear parietal cells remained attached to each other and became shrunken to form a ghost architecture of the liver. The wall of the hepatic veins and the von Kupffer cells resisted the necrotizing influence of paracetamol but eventually degenerated. The histopathology in other organs is listed in Table 7.

TABLE 7

HISTOPATHOLOGIC FINDINGS IN ALBINO RATS WHICH DIED FROM ORAL ADMINISTRATION OF PARACETAMOL

Organ	Death at less than 24 hr	Death at 1 to 7 days
Adrenal glands	Sinusoidal congestion	Enlarged, normal structure
Brain	Mild meningeal congestion	Minute areas of granular degeneration
Gastrointestinal tract:		
Cardiac stomach	Submucosal capillary-venous congestion	Normal
Pyloric stomach	Capillary-venous congestion	Occasional ulcer
Small bowel	Minor capillary-venous congestion	Normal
Cecum	Capillary-venous congestion	Normal
Colon	Capillary-venous congestion	Normal
Heart	Normal	Vacuolar degeneration of coronary arterioles
Kidneys	Capillary congestion; tubular oedema	Tubular, papillary and interstitial oedema; tubular casts and degeneration
Liver	Centrilobular congestion and pale-staining	Centrilobular necrosis and general hepatic necrosis
Lungs	Congestion and venous thrombosis	Normal
Muscle (ant. abd. wall)	Normal	Normal
Salivary glands (submax.)	Interstitial oedema; hypogranulation of serous glands	Obliteration of lumen of serous glands; dilated ducts; venous thrombosis
Skin	Normal	Mild subcutaneous congestion
Spleen	Red pulp contracted	Red pulp contracted; vacuolation of splenic arteriolar media
Testes	Interstitial congestion	Normal
Thymus gland	Capillary-venous congestion	Loss thymocytes
Thyroid gland		Dilated follicles; flat epithelium

Recovery in survivors was accompanied by restoration to or toward normal of the growth rate, food intake, water intake and colonic temperature (Table 2). At 3 days the listlessness, decreased response to stimuli, tremor, tail extension and pallor had disappeared (Table 3) and this was accompanied by a diuresis and alkalinuria (Table 2). At 1 month, body weight and organ weights had returned to normal limits (Table 5) and organ water levels were normal or slightly below normal (Table 6).

DISCUSSION

If the bulk of orally administered phenacetin is converted into paracetamol in rats, as it is in man (Lorenzen, 1962), the acute oral toxicity of paracetamol in rats would be expected to be like that of phenacetin. The results were compared, therefore, with

previous results obtained in this laboratory on the acute oral toxicity of phenacetin (Boyd, 1959). In the latter study the technique was identical but female, rather than male, rats were used.

The LD50 $\pm$ S.E. of paracetamol (3.71 $\pm$ 0.83 g/kg) was significantly higher than that of phenacetin (1.65 $\pm$ 0.35 g/kg). This difference may have been due in part to the use of females and somewhat older animals in the phenacetin study but others (Smith, 1958) have found a similar difference in the LD50. The difference could be due to a species variation in the extent of de-ethylation of phenacetin or to differences in the rate of gastrointestinal absorption. Paracetamol has been reported slowly absorbed from the rat stomach and intestines (Weikel & Lish, 1959). The mean interval to death from paracetamol (21 hr) was practically the same as that from phenacetin (23 hr—Boyd, 1959).

The hypothermic stupor seen in rats given paracetamol also occurred following phenacetin (Boyd, 1959). Loss of organ weight and water content were in general somewhat greater following paracetamol than following phenacetin. This could have been due to the hypertonic action of the larger lethal dose since similar changes occur in rats given lethal doses of sucrose and various salts (Boyd. Godi and Abel, 1965).

Death from phenacetin was also accompanied by a generalized capillary-venous congestion with tubular nephritis and early centrilobular hepatic necrosis. The extensive hepatic necrosis after paracetamol was not seen after phenacetin, possibly because it was not looked for as all delayed deaths from phenacetin occurred at night and complete autopsies were not performed. Liver necrosis is not listed as a toxic effect of phenacetin or paracetamol in man (Lozinski, 1963), but Smith (1958) in his review quotes two case reports of patients who died from excessive use of phenacetin, one with signs suggestive of "basic biliary tract disease" (p. 128) and a second with cirrhosis of the liver (p. 131).

Barnes and Paget (1965) have reviewed evidence on the series of events leading to hepatic necrosis by drugs which accumulate in the liver. The fact that paracetamol in large but not lethal doses tends to accumulate in liver tissue water (Smith, 1958; Gwilt, Robertson & McChesney, 1963) might have indicated that liver necrosis should be looked for in animals given lethal doses. Actually what prompted us to look for liver necrosis was recent experience in this laboratory with liver necrosis produced by oral administration of tannic acid (Boyd, Bereczky & Godi, 1965).

Finally it should be emphasized that while liver necrosis could be proved as one cause of death from paracetamol in this study, it was but part of the syndrome of acute toxicity. It could be proved only in some 10% of the animals which died, 10% in which death was sufficiently delayed for liver necrosis to have time to develop. It may have been a factor in the early deaths associated with hypothermia and generalized capillary-venous congestion. Likewise in acute tannic acid poisoning, liver necrosis is only a part of the syndrome of intoxication (Boyd, Bereczky & Godi, 1965). Liver necrosis has been noted in the title of this communication, therefore, simply because it was a rather unique feature of our findings on the acute oral toxicity of paracetamol.

SUMMARY

1. The objective of this project was to determine the clinicopathologic syndrome of acute oral toxicity to paracetamol in albino rats and to compare the results with those previously determined for phenacetin.

2. The oral LD50 $\pm$ S.E. of paracetamol was found to be 3.71 ± 0.83 g/kg which was significantly higher than 1.65 ± 0.35 g/kg reported for phenacetin.

3. The syndrome of intoxication during 24 hr after giving paracetamol was similar to that following phenacetin. Death was due to respiratory failure in deep hypothermic stupor and was accompanied by extensive capillary-venous congestion, centrilobular hepatitis and tubular nephritis.

4. When death occurred at 1–7 days, the centrilobular hepatitis was found to develop gradually into hepatic necrosis which was accompanied by degenerative changes in the brain, kidneys and arterioles. Delayed deaths had not been as extensively studied in rats given phenacetin so that while hepatic necrosis was not reported, it may have been present.

5. Recovery in survivors of paracetamol intoxication was similar to that following phenacetin. Signs of recovery appeared in the second or third day.

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