SUMMARY

The aim of this work was to investigate the effect of chloramphenicol and phenylbutazone on the foetuses of an inbred strain of the albino mouse, when each drug was maternally administered during different periods of embryonic development.

The systems of inbreeding adopted were; self-fertilization, brother and sister mating, and double first cousin mating.

In the pertinent literature, the judgement that a drug can affect the embryonic development was based mainly on morphological studies. The present investigation comprised morphological examination of the foetuses obtained, macroscopic examination of the foetal skeleton made visible by clearing technique, and microscopic examination of serial sections of the liver, kidney and spinal cord. The number of foetuses per litter, the number of living, dead and abnormal foetuses were also recorded.

This study covered the whole period of pregnancy divided into three trimesters. Pregnant females were divided into three groups, the first
group was treated daily from the 1st to the 6th, the
second group from the 7th to the 12th, and the third
group from the 13th to the 18th day of gestation.
Each group of pregnant females was treated by a low
and a relatively higher dose of the drug, and each
dose was administered by three routes; oral, intra-
muscular and intraperitoneal. However, phenylbutazone
caused severe tissue reaction when administered by the
intramuscular route and sudden death when administ-
ed by the intraperitoneal route, and consequently the
oral route was adopted.

The control animals were of the same inbred
strain of the treated animals. The controls were put
under the same conditions as the test animals; they
were given the drug solvent only, by the same route
of administration. The incidence of spontaneous
malformations was not observed during the breeding of
the mice used in order to get a large number of inbred
strain of animals. Moreover, no deviation from
normal was observed among foetuses extracted from
the control females.
The results obtained show that chloramphenicol has no major effect on the embryonic development of the albino mouse. The anomalies obtained are probably not due to impairment of organogenesis but may be related to later interference with the development of the limbs. The malformed foetuses were from females administered the higher dose of chloramphenicol by the oral route. This offered an evidence that vitamin deficiency may be responsible for the anomalies observed. Malformed foetuses were obtained from females treated during mid-or late gestation. The abnormal foetuses were smaller in size than the controls. The malformations were restricted to the fore and hind limbs. The affected limbs showed brachymelphy and brachydactyly. In most cases the limbs were flexed away from their normal position.

Examination of the foetal skeleton, among the group subjected to chloramphenicol, showed that the long bones were all present although shorter in the affected limbs. Among the small bones some caudal vertebrae, the astragalus and the calcaneous bones were frequently missing.
Chloramphenicol affected the liver cells of the foetuses with varying severity, since they showed the different phases of cell degeneration. The pathological changes were cloudy swelling, hydropic degeneration, fatty degeneration, necrosis, bile pigment retention and lymphocytic infiltration. No marked difference was observed between the pathologic changes caused by 1/10 or 1/3 LD\(_{50}\). It seemed that the lower dose was enough to produce these degenerative changes.

Chloramphenicol was found to affect the convoluted tubules and the ascending limbs of Henl's loops of the foetal kidney. Degenerative changes such as cloudy swelling and necrosis appeared in the lining cells of these affected tubules. However, the glomeruli, collecting tubules and the descending limbs of Henl's loops appeared normal.

No structural changes related to maldevelopment were observed in either kidney or liver of foetuses subjected to chloramphenicol.

Treatment during early gestation with 1/10 or 1/3 LD\(_{50}\) of chloramphenicol caused asymmetry in the
foetal spinal cord. The asymmetry was due to herniation in the gray matter, white matter and meninges. These malformations in the spinal cord were reflected on the vertebral arch, which was destructed and showed deficiency at the regions of the affected cord.

Treatment during mid-gestation with 1/10 or 1/3 LD$_{50}$ of chloramphenicol caused marked shrinkage of the foetal spinal cord inside the dura mater. Consequently, a large subdural space was present and the outline of the spinal cord was crenated. In spite of these changes the spinal cord remained symmetrical. The vertebral canal was intact and no haemorrhages were detected.

Treatment during late gestation with 1/10 or 1/3 LD$_{50}$ of chloramphenicol resulted in ruptures of the walls of the dorsal and ventral spinal arteries and thus subdural haemorrhages were produced. These haemorrhages pressed upon the outer surface of the spinal cord causing subdural invaginations. Destruction of the gray and white matter of the cord was also observed. The vertebral arch was consequently destructed in the regions of the affected cord.
Malformations of the spinal cord were restricted to the cervical and thoracic regions.

The females administered phenylbutazone were susceptible for abortion, specially those subjected to treatment during early gestation. In this group 10 per cent were aborted among females treated with 100 mg per kg and 30 per cent among those treated with 200 mg per kg. No malformations were observed by treatment with the lower dose. Malformations were obtained by treatment with the higher dose during early and mid-gestation.

No major malformations were obtained among foetuses subjected to phenylbutazone treatment. The abnormal foetuses were markedly smaller in size. The malformations were restricted to the limbs and the body axis. The fore-limbs were more affected, and the affected limbs showed atrophy, brachymel and brachydactyly. In most cases the limbs were flexed away from their normal position. The body axis was markedly bent ventrally in some of the abnormal foetuses.

Phenylbutazone showed no major effect on the embryonic development of the skeleton. However, the
caudal segments were absent in some cases. The long bones were all present and were shorter than normal in the affected limbs. Some of the caudal vertebrae, the astragalus, and the calcaneous bones were frequently missing.

Phenylbutazone caused degenerative changes in the foetal liver that ranged from cloudy swelling to complete necrosis of the liver cells. The drug also caused patchy fibrosis of the liver in foetuses subjected to treatment during late development. The lower dose (100 mg per kg) was enough to cause these degenerative changes.

Phenylbutazone was found to cause degenerative changes such as cloudy swelling and necrosis in the lining cells of the convoluted tubules and the ascending limbs of Henl's loops. In some cases the drug caused congestion of the glomeruli and straight vessels of the medulla with haemorrhages in the capsular and cortical areas. The lower dose of the drug was enough to cause these pathological changes.

No structural changes related to maldevelopment were observed in either the kidney or the liver.
of foetuses subjected to phenylbutazone during development.

Phenylbutazone had no effect on the foetal spinal cord when it was administered during early gestation. Treatment during mid-gestation by 100 mg per kg caused splitting of the spinal cord from the dorsal side till the region of the central canal. Treatment during late gestation with phenylbutazone caused degenerative changes in the gray and white matter of the spinal cord and consequently they were reduced in some regions. The drug also affected the duramater as it was disrupted in some regions. Subdural haemorrhages from the dorsal and the ventral spinal arteries pressed upon the surface of the spinal cord and caused invaginations in some areas.