

THIOURACIL ADMINISTRATION AND THYROIDECTOMY IN EXPERIMENTAL POLYARTHRITIS OF RATS*

BY

HELEN B. TRIPI, WILLIAM C. KUZELL, and GRACE M. GARDNER†

*From the Department of Pharmacology and Therapeutics, Stanford University School of Medicine,
San Francisco, California*

Many clinical reporters have alluded to the possible influence of the functional state of the thyroid gland in rheumatic disease. Several have reported the coincidence of hyperthyroidism and rheumatoid arthritis (Snorrason, 1943; Duncan, 1928, 1932; Garrod, 1906; Jones, 1909; Spriggs, 1908; Thiroloix and others, 1926; Bauer and others, 1940), the coincidence of rheumatic fever and hyperthyroidism (Schjødt, 1943), and relationship of thyroid hypofunction to degenerative joint disease or osteo-arthritis (Hall and Monroe, 1932-3; Falcone and Delbene, 1945). Some have observed that the basal metabolism is increased more often in rheumatoid arthritis than in degenerative joint disease or mixed arthritis (Rawls and others, 1938). Others have doubted that thyroid dysfunction had any marked influence on arthritis in general (Bauer, 1939; Pemberton and Tompkins, 1920; Freyberg, 1942). Patients have been observed to develop a clinical picture resembling rheumatoid arthritis following thyroidectomy (Monroe, 1935). Hypertrophic pulmonary osteo-arthropathy after thyroid-

ectomy has been previously reported (Cushing, 1937; Ryneerson and Sacasa, 1941).

Accordingly there seems to be considerable clinical evidence and continued suspicion that the thyroid gland is in some way implicated in arthritis. Therefore it seemed desirable to us to determine whether thyroidectomy had an influence on the course of experimental polyarthritis and whether such changes were due to lowering of the basal metabolic rate or to ablation of the gland itself. No previous effort has been made to determine the influence of the thyroid on the course of experimental arthritis of any kind. Polyarthritis in rats and mice has been used in recent years as a method of evaluating chemotherapeutic agents (Collier,

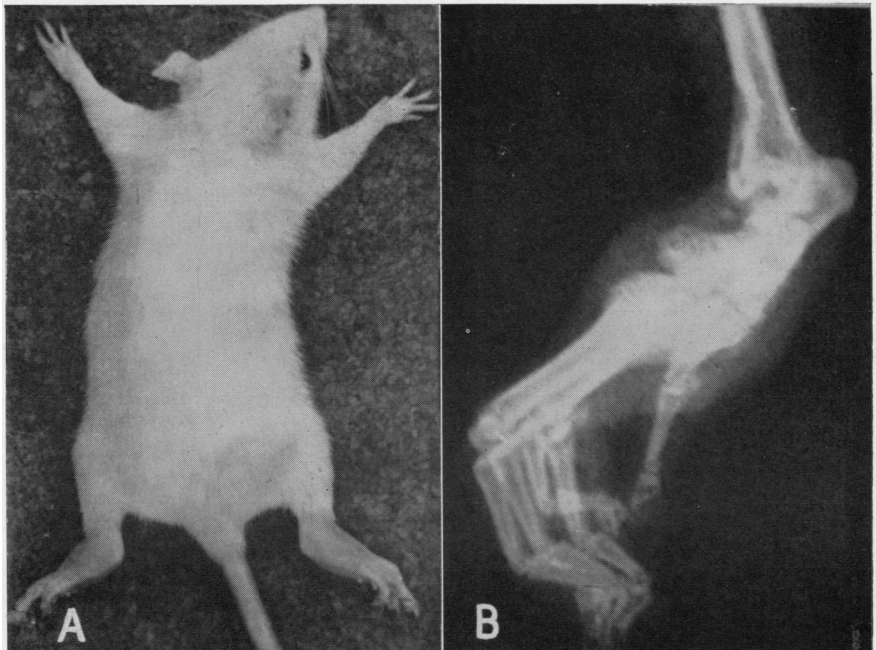


FIG. 1.—Albino rat showing (A) polyarthritis two weeks after intraperitoneal inoculation of 2 c.cm. broth culture of L4 strain of pleuropneumonia-like organisms, and (B) radiograph showing arthrodeseis of tarsal joints two months after inoculation.

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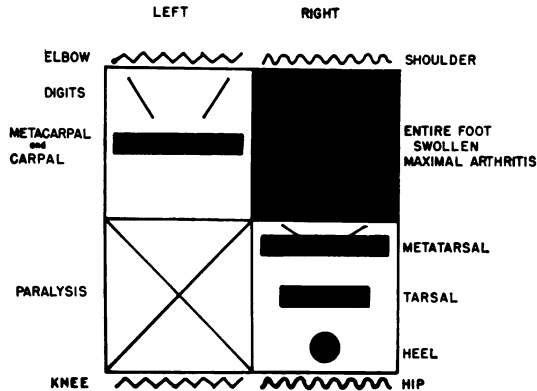


FIG. 2.—Arthrogram for recording the extent of joint involvement in experimental polyarthritis of rats.

1939 a and b; Findlay and others, 1939 and 1940; Sabin and Warren, 1940a and b, 1941; Sabin and Morgan, 1940; Snow and Hines, 1941; Sabin, 1942; Preston and others, 1942; Powell and Rice, 1944; Powell and others, 1946; Browning and Rice, 1947; Tripi and Kuzell, 1947). While the pathological picture is not the same as that in rheumatoid arthritis in man, the experimental arthritis produced by the L4 strain of pleuropneumonia-like organisms in rats and mice is amenable to chrysotherapy. Fig. 1 shows a rat with arthritis produced by the intraperitoneal inoculation of 2 c.cm. of a broth culture of the L4 strain, of pleuropneumonia-like organisms. This experi-

mental arthritis is, at present, the procedure of choice for the study of factors which may influence the course of joint disease. Our objective was to determine whether reduction of the metabolic rate by prolonged administration of thiouracil, or by thyroidectomy, would alter the incidence and severity of rat polyarthritis due to pleuropneumonia-like organisms of the L4 strain (P.L.O.)*. This paper presents the results obtained.

Methods

Albino rats were used throughout and, whenever possible, the numbers of males and females were equal. All unmedicated animals were allowed to eat ground purina dog chow checkers† (basic diet) and to drink water freely.

The experimental polyarthritis was produced by inoculating each animal, intraperitoneally, with 2 c.cm. of an 18- to 24-hour culture of P.L.O. The microbes were grown as a routine on agar or in broth media consisting of a buffered yeast-extract-tryptose base enriched with 10 per cent. of Seitz-filtered horse serum to which 2 per cent. of agar was added for the solid medium (Tripi and Kuzell, 1947). Before inoculation all animals were weighed once weekly, and after inoculation the weighing schedule coincided with the examination of the animals for arthritis. Food consumption was recorded at least twice weekly (usually three times), and daily during the week following inoculation.

* Abbreviation of pleuropneumonia-like organisms of the L4 strain used throughout this paper.

† Purina dog chow checkers are compressed pellets containing: protein 21 per cent., fat 4 per cent., fibre 6 per cent., nitrogen-free extract 46 per cent., and ash 9 per cent.

TABLE I
SCORE EVALUATION ACCORDING TO DEGREE AND EXTENT OF RAT
POLYARTHRITIS FOR EACH EXTREMITY

Score	Degree	Extent of arthritic involvement
0	None	None.
1	Minimal	Swelling only in toe joints, or transitory swelling of any single joint, or lasting weakness of an extremity with the involved joint, or joints, undetermined.
2	Moderate	Swelling of 4, or more, toe joints, or severe and lasting involvement of a single large joint, or several small joints, or paralysis of a foot due to involvement of the wrist or heel without swelling.
3	Severe	Extensive, and lasting, involvement of several joints (maximal for the anterior extremities) followed by ankylosis.
4	Severest	Extensive involvement of joints in all regions of a foot with extreme swelling of an entire foot followed by ankylosis. In the anterior extremities, maximal involvement plus involvement of the elbow or shoulder.
5	Severest	Same as Score 4 plus involvement of the knee or hip.

During the week following inoculation the animals were examined daily for symptoms of joint involvement, on alternate days during the second week, twice during the third week, and once weekly thereafter. At each examination, a diagrammatic record (arthrogram, Fig. 2) of the location and degree of involvement of affected joints of the extremities was made according to a slight modification of the method of Sabin and Warren (1940b).

At the end of an experiment, all arthrograms for each rat were compiled into a single composite arthrogram which was given a numerical score according to the recorded number of affected joints and the degree to which they were involved. The score values ranged from 0 to 4 for each anterior extremity and from 0 to 5 for each posterior extremity; thus the arthrogram score for any individual rat lay within a range of 0 to 18, 0 indicating no demonstrable signs of arthritis, and 18 indicating that all four extremities were involved to a maximum degree (Table 1). This method of scoring was purely arbitrary, being intended as a rough quantitative clinical estimation of the macroscopic joint involvement. There was little difficulty in scoring minimal and maximal degrees of arthritis, but between these extremes the score depended largely on the judgment of the observer.

At death, or when experiments were terminated after 4 to 6 months, all animals underwent autopsy examination. All lesions found were examined bacteriologically, whether they were in the joints or the viscera. Animals which had shown joint involvement were radiographed to demonstrate the extent of arthritic changes.

The effects of thiouracil on experimental polyarthritis were observed in rats weighing approximately 100 g. Thiouracil was used in a concentration of 0.1 per cent. incorporated into the basic ground diet by mixing for 30 minutes with a mechanical mixer. Unmedicated controls received the basic diet. At the end of five, seven, and twelve weeks, groups of rats on the thiouracil diet, with their respective controls, were inoculated with P.L.O. In the *first* and *second* series, inoculated after five to seven weeks respectively, half the animals were changed to the basic diet at the time of inoculation. A group of controls equivalent in weight to the thiouracil-animals was also inoculated. Since the results subsequently obtained did not warrant continuation of these procedures, all animals of the third series were kept on the thiouracil diet after being inoculated at the end of twelve weeks. No inoculation-weight controls were used. Forty rats receiving the thiouracil were not inoculated and served as a control group for comparison with the uninoculated unmedicated controls, all inoculated animals, and those removed from the thiouracil diet at the time of inoculation with P.L.O.

Thyroidectomies were performed on a group of thirty rats for comparison regarding the degree of hypothyroidism caused by the prolonged administration of thiouracil. Both the thyroidectomized animals and their controls with thyroids intact received the basic diet supplemented with milk in order to overcome calcium imbalance caused by unavoidable removal of

the parathyroids along with thyroid gland. Groups of thyroidectomized animals were inoculated twenty-five, seventy, and eighty-six days after operation.

Periodically, the oxygen consumption of normal, thyroidectomized, thiouracil-medicated, arthritic-thiouracil-medicated, and arthritic rats was determined according to the procedure of Tainter and Rytand (1934). Surface area was calculated according to the formula $S. A. = 9.1 \times W^{2/3}$, after Benedict (1934).

Blood was examined in rats on thiouracil and their controls. Care was used to prevent excitation of the animals while blood was being taken. Once weekly, from the beginning of an experiment and during a period of seventy-two days, total leucocyte and differential leucocyte counts were made on the blood of animals in the first two groups and their respective controls selected at random from each group, but this was done infrequently since all values obtained were normal.

Toxic agents, chemically and physically different from thiouracil, were administered in order to determine whether toxicity in general had any effect on the development of arthritis in rats inoculated with P.L.O. This was done to aid in evaluating any possible specific toxic effects of thiouracil in enhancing this type of experimental arthritis. The following drugs were used: phenobarbital sodium, 0.1 per cent. in the basic diet (Hanzlik and Laqueur, 1946), arsenic trioxide, 0.01 per cent. in drinking water (Lehman and Chase, 1944). On the fourteenth day of medication all animals were inoculated with P.L.O.

The details of all changes were summarized in tables or curves for comparison; however, most of these have been omitted here since minor differences revealed nothing significant with respect to the principal objective, or fell within range of variations in the different groups of animals. The most important result obtained, the increased severity of the polyarthritis caused by the thiouracil, may now be discussed.

Changes in Joints of Polyarthritic Thiouracil-Medicated and Thyroidectomized Rats

Thiouracil-Medicated Rats.—A numerical representation of the degree of joint involvement of inoculated and thiouracil-treated rats and their controls is shown in Table 2, and the percentage incidence of arthritis and deaths among these animals in Table 3. It is evident that the incidence and degree of arthritis in animals inoculated with P.L.O. after thiouracil medication for thirty-four to fifty-one days was not significantly different from that of the controls. Polyarthritis failed to develop in many of these animals. The greatest degree of arthritis involvement was obtained with the combination of continued thiouracil administration and inoculation of the animals after eighty-five days of thiouracil medication, but the mortality was somewhat greater among these animals, 18 per cent. as compared with 13 per cent. in rats inoculated after fifty-one days on thiouracil. All the thiouracil animals became

TABLE 2

COMPOSITE ARTHROGRAM SCORES FOR THIOURACIL MEDICATED AND CONTROL RATS FOLLOWING INOCULATION WITH PLEUROPNEUMONIA-LIKE ORGANISMS (L4 STRAIN)

	P.L.O.* alone (controls)		Continued thiouracil† with P.L.O.*		P.L.O.* preceded by thiouracil	
	Males	Females	Males	Females	Males	Females
					34 days of thiouracil	
No. of rats	10	10	8	8	7	7
Per cent. dead	0	10	25	50	57	87
Composite arthrogram score . .	5.3	4.9	3.1	5.0	3.6	2.2
					51 days of thiouracil	
No. of rats	6	10	6	10	10	10
Per cent. dead	0	20	17	10	0	0
Composite arthrogram score . .	4.4	3.3	3.2	3.7	3.8	3.6
					85 days of thiouracil	
No. of rats	15	15	17	17	—	—
Per cent. dead	7	13	12	24	—	—
Composite arthrogram score . .	4.0	3.6	8.0	5.0	—	—

* Inoculation with pleuropneumonia-like organisms (L4 strain).

† For variable periods up to 233 days (see text).

TABLE 3

PERCENTAGE INCIDENCE OF ARTHRITIS AND DEATHS AMONG THIOURACIL-TREATED AND UNTREATED RATS FOLLOWING P.L.O.* INFECTION

Experimental groups	Incidence of arthritis (%)	Deaths			
		Total (%)	Early (within 4 days) (%)	Late (infected non-arthritic) (%)	Late (arthritic) (%)
<i>Group 1, P.L.O.* inoculated after 34 days of thiouracil:</i>					
(1) No thiouracil	100	5	0	0	5
(2) Thiouracil continued throughout . .	60	38	25	13	0
(3) Thiouracil discontinued after P.L.O.	65	71	7	29	35
<i>Group 2, all inoculated* at 51 days thiouracil:</i>					
(1) No thiouracil	100	13	0	0	13
(2) Thiouracil continued throughout . .	81	13	0	13	0
(3) Thiouracil discontinued after P.L.O.*	100	0	0	0	0
<i>Group 3, all inoculated* at 85 days thiouracil:</i>					
(1) No thiouracil	97	10	0	3	7
(2) Thiouracil continued throughout . .	100	18	0	0	18

* Inoculation with pleuropneumonia-like organisms (L4 strain).

TABLE 4

INCIDENCE AND SEVERITY OF ARTHRITIS AND PERCENTAGE OF DEATHS AMONG INOCULATED RATS AFTER CONTINUED ADMINISTRATION OF ISOPROPYL ALCOHOL PHENOBARBITAL AND ARSENIC TRIOXIDE

Drug	Mortality before inoculation (%)	Mortality after inoculation (P.L.O.)*			Incidence of arthritis (%)	Composite arthro-gram score	
		Total (%)	Early (infected < 4 days) (%)	Late (infected non-arthritic) (%)			Late (infected arthritic) (%)
Unmedicated controls ..	0	45	10	0	35	100	4.9
Isopropyl alcohol ..	40	50	0	17	33	75	3.6
Phenobarbital sodium ..	50	40	0	0	40	100	4.9
Arsenic trioxide ..	15	18	0	0	18	88	5.2

* Pleuropneumonia-like organisms (L4 strain).

arthritic, and there was a significant increase in the degree of joint involvement among these animals as compared with their controls.

There was a greater mortality among all thiouracil-treated rats than among the controls, the mortality being highest among those inoculated after five weeks. Among these latter rats the percentage of deaths was greater among the animals removed from the thiouracil diet to the control diet at the time of inoculation, and was further increased for the females as compared with the corresponding males. The reason for the increased mortality among the treated animals inoculated after five weeks was considered not to be due to greater virulence of the culture used for inoculation of the rats, but rather to increased susceptibility of the host to the microbes (a false enhancement of the virulence of the culture) brought about by the disturbed metabolism of the rats. In all groups, animals which died within the first few days after inoculation were usually free of joint swellings, the cause of death being invariably peritonitis. The rats which died later exhibited joint swellings, but the cause of death was presumably due to overwhelming infection manifested by the widespread distribution of small abdominal abscesses and, less often, pulmonary abscesses. The distribution and size of the abscesses was dependent upon the length of time which had elapsed since inoculation. Sixty per cent. of the animals sacrificed at the end of the experimental period exhibited such abscesses, and in most instances the lesions were

hard and large, often 1 to 2 cm. in diameter, and heavily encapsulated; and the grey-white, friable material within the capsule yielded pure cultures of P.L.O. The microbes were recovered at autopsy from the brain, lungs, spleen, liver, abdominal abscesses, testes, and prostate gland of two animals. It was possible invariably to recover regularly the microbes from the peritoneal exudate four days after inoculation; they were recovered from ankylosed joints in three rats five months after inoculation. Animals which had received thiouracil showed the same lesions as the unmedicated animals, but approximately 80 per cent. of these had gross visceral lesions at autopsy. Thus, in general, the suggested greater severity of the polyarthritis during the life of thiouracil-medicated rats was also manifested by the presence of more severe and extensive pathological lesions at autopsy.

Thyroidectomized Rats.—Neither the rates of growth nor food consumption of thyroidectomized rats differed significantly from those of the controls. Leucocyte counts were not made prior to thyroidectomy, but counts done at intervals following thyroidectomy and inoculation did not differ in any significant respect from those of the controls.

There were no deaths among thirty thyroidectomized animals inoculated with P.L.O., at 25, 70, and 86 days after thyroidectomy. The incidence of arthritis among control animals was 100 per cent., and among thyroidectomized animals 95 per cent. The averages of the arthro-gram scores for control and thyroidectomized males were practically the

same, i.e. 3.2; for the female controls the average was 3.8, and for the thyroidectomized females 3.6. Therefore, lack of thyroid function could not have been responsible for the suggested increase in severity of the polyarthritis produced by thiouracil.

Other Toxic Agents.—The arthrogram scores, per cent. mortality, and incidence of arthritis in inoculated rats after continued administration of phenobarbital (fourteen weeks), isopropyl alcohol (fourteen weeks), and arsenic trioxide (four weeks) are shown in Table 4. The estimated average daily doses of these drugs for each rat were as follows: 0.05 c.cm. (males) and 0.03 c.cm. (females) of isopropyl alcohol, 2.0 mg. (males) and 1.4 mg. (females) of arsenic trioxide, and 15.0 mg. (males) and 10.0 mg. (females) of phenobarbitone.

It is seen that the incidence and severity of the arthritis among these three groups of medicated animals inoculated with P.L.O. was generally not greater than that for the unmedicated controls. In fact mortality was appreciably less in rats receiving isopropyl alcohol (75 per cent.) and arsenic trioxide (88 per cent.). The mortality before inoculation among animals receiving isopropyl alcohol and phenobarbital alone, 40 and 50 per cent. respectively, suggested the possibly greater toxicity of these compounds as compared with thiouracil alone (2 per cent.). The uniform, though generally depressed, rate of gain in weight for animals receiving isopropyl alcohol, phenobarbital, and arsenic trioxide was in marked contrast to the early normal rate of gain which became abruptly levelled off and was followed by a minimal rate of gain as in thiouracil-poisoned animals. Besides reduction of body weight there were also some decreases in food consumption and some mortality in all three groups, in confirmation of previous investigations of isopropyl alcohol by Lehman and Chase (1944), of arsenic trioxide by Sollmann (1921), and of phenobarbitone by Hanzlik and Laqueur (1946). Since the chronic toxicity of these physically and chemically different drugs did not increase the severity of the experimental polyarthritis, even though they appeared to be more toxic than thiouracil, the thiouracil medication seemed to predispose to greater severity of the arthritis in some peculiar way. Our results with inoculated rats medicated with isopropyl alcohol, arsenic, and phenobarbital are somewhat vitiated by the fact that fewer animals of these groups survived for comparable determination of the incidence of arthritis among those on thiouracil. At least it can be said that the numbers of rats on these drugs were considerable, yet their toxic actions did not seem to increase the severity of the arthritis.

Other Changes in Thiouracil-Medicated and Inoculated Rats

Changes in body weight, leucocyte counts, differential counts, and food consumption in inoculated unmedicated controls and in thiouracil-medicated and inoculated (P.L.O.) rats were practically the same. There were temporary fluctuations in these functions and elements, often decreases, if anything, at the beginning of an experiment, followed by recoveries to pre-medication, or pre-inoculation, levels on the fourth day. From there on to the conclusion of the experiments any changes were minor or insignificant except for growth, which generally increased in all animals. The somewhat greater loss of body weight in thiouracil-medicated and inoculated rats was probably due to decreased food consumption, since they ate about 10 per cent. less food during this time. There is no good reason to believe that these temporary and often comparatively minor changes contributed significantly to the increased severity of the polyarthritis under thiouracil. This suggested that the increased severity of the arthritis was the result of some intrinsic systemic action of the thiouracil.

As might be expected the basal metabolic rate of the fourteen thiouracil-medicated rats was reduced to 58 per cent. of the basal metabolic rate of forty uninoculated unmedicated rats. The metabolic rate was reduced by the same amount in twenty thyroidectomized rats and twenty arthritic, thiouracil-medicated rats, but it was about 80 per cent. of normal in six unmedicated arthritic rats. Neither sex nor age of these rats influenced the basal metabolic rate.

The thyroid glands of rats which had received thiouracil for 233 days, with or without P.L.O., showed about a 500 per cent. increase in weight, with a tendency to slightly lower weights in those rats on thiouracil and P.L.O. No significant sex difference in the average per cent. weights of thyroids of normal or medicated rats was observed. Histologically, the thyroids of rats inoculated with P.L.O. only were normal; whereas those of thiouracil-medicated rats were diffusely hyperplastic, devoid of colloid, and after prolonged thiouracil medication showed nodular hyperplasia dependent in degree on the duration of medication (Kuzell and others, 1948). The relationship of size and extent of histological changes in the thyroid to duration of thiouracil medication is supported by the results of several investigators, chiefly by those using periods up to a hundred days, and by one or two others using periods of 205 days or longer where the relative size of the gland was 350 per cent.

(females) and 500 per cent. (males) (Thyssen, 1947), an order of magnitude confirmed by us. Clearly our rats responded typically to thiouracil. A separate report on the endocrines of the rats in this study is to be made by Dr. G. L. Laqueur of the department of pathology in this university.

Summary and Conclusions

1. Albino rats receiving thiouracil in the diet for periods from 120 to 233 days developed hyperplastic thyroids with nodular hyperplasia. When infected at the end of eighty-five days of such medication with the L4 strain of pleuropneumonia-like organisms these animals developed a suggestively greater severity of polyarthritis than did the controls, and showed greater mortality.

2. Thyroidectomized albino rats which had an average basal metabolic rate of only 58 per cent. of normal (the same as for the thiouracil-medicated rats), when infected with the L4 strain of pleuropneumonia-like organisms developed polyarthritis which was the same as that of the controls. Presumably, therefore, lack of thyroid does not affect the course of this polyarthritis.

3. Albino rats poisoned with agents chemically and physically different from thiouracil, namely, arsenic trioxide, isopropyl alcohol, and phenobarbital, showed no increase in severity of polyarthritis due to the L4 strain of pleuropneumonia-like organisms.

4. Thus the suggested increase in severity of this experimental polyarthritis in thiouracil-medicated animals for the largest period (eighty-five days) is believed to be due to some peculiar intrinsic action of the thiouracil.

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Administration de Thiouracile et Thyroïdectomie dans la Polyarthrite expérimentale chez le Rat

RÉSUMÉ ET CONCLUSIONS

1. Des rats blancs recevant du thiouracile dans leur alimentation pendant 120 à 233 jours, ont présenté une hyperplasie thyroïdienne nodulaire. Lorsque ces animaux avaient été infectés après 85 jours de ce traitement par une souche L4 de microbes du type pleuropneumonique, ils ont présenté une polyarthrite dont la gravité était nettement plus grande que chez les animaux témoins, et leur mortalité était plus élevée.

2. Des rats blancs thyroïdectomisés dont le métabolisme basal était en moyenne 58 pour cent de la normale (le même que chez les rats traités au thiouracile), inoculés avec la souche L4 de microbes du type pleuropneumonique ont présenté une polyarthrite semblable à celle des témoins. L'absence de thyroïde ne semble donc pas affecter l'évolution de cette polyarthrite.

3. Des rats blancs traités par des substances toxiques différentes du thiouracile aux points de vue chimique et physique, tels que l'anhydride arsénieux, l'alcool isopropylique, et le gardénal, n'ont présenté aucune augmentation de la gravité de la polyarthrite provoquée par la souche L4 de microbes du type pleuropneumonique.

4. Il est donc probable que la gravité accrue de cette polyarthrite expérimentale chez des animaux recevant du thiouracile pour le période la plus longue (quatre-vingt-cinq jours) est due à une action particulière du thiouracile.