metabolism of the animals receiving methylthiouracyl remained absolutely unchanged.

The daily injection of 10 micrograms increases also $O_2$-consumption of thiouracyl-treated animals, yet, while in the untreated thyroidectomized rat the rate of metabolism rises within 24 hours after the first thyroxin injection and remains elevated for 6 days following the termination of thyroxin administration, $O_2$-consumption of thiouracyl-treated animals increases only after the third dose of thyroxin and approximates the original level days before the rate of metabolism of the untreated animal returns to its initial value.

*Conclusions.* It could be demonstrated that methylthiouracyl inhibits the action of small doses of thyroxin completely in the thyroidectomized animal. Therefore it is evident that its action cannot be limited to suspending the synthesis of thyroxin in the thyroid gland, and it must be assumed that at least it inhibits the action of thyroxin in other tissues as well. Considering that very probably the amounts of thyroxin employed in these experiments fall within the range produced by a normal and possibly even by a hyperactive thyroid gland, the question arises whether it is absolutely necessary to assume that the principal pharmacological action of antithyroid drugs is the inhibition of thyroxin synthesis. The most direct evidence in favour of the inhibition of thyroxin synthesis was furnished by CHAIKOFF and coworkers (l. c.) in experiments demonstrating that antithyroid drugs inhibit the formation of organic iodine compounds by thyroid slices *in vitro*. The fact that thyroids of thiouracyl-treated animals are poor in iodine, retain iodine only for a short time, and do not contain organic iodine after administration of iodine carries much less weight, for essentially similar findings can be obtained in hyperactive glands. The experiments reported of course do not disprove the inhibition of thyroxin synthesis by antithyroid drugs, yet they demonstrate clearly the existence of another mechanism capable of accounting even in the presence of physiological amounts of thyroxin for the production of a state of hypothyroidism by antithyroid drugs. The assumption of a fundamentally different action of thiouracyl on the thyroid (inhibition of thyroxin synthesis) and other tissues (inhibition of the action of thyroxin) is rather unsatisfactory, and probably further investigation will furnish an explanation based on a single mechanism. In any case the inhibiting action of methylthiouracyl on the action of thyroxin cannot be disregarded in future attempts to analyse the action of this and similar drugs.

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*Zusammenfassung*

Kleine Thyroxingaben (1–5 μg pro Tag), die den Stoffwechsel schilddrüsenloser Ratten bedeutend erhöhen, sind bei Tieren, die mit Methylthiouracil behandelt wurden, völlig unwirksam. 10 μg täglich verursachen auch im thiouracilbehandelten Tier eine Steigerung des Sauerstoffverbrauches. Dessen Höhe und Dauer bleibt aber weit hinter der eines unbehandelten Tieres zurück. Es wird damit bewiesen, daß Thiouracil *peripher* Thyroxindosen von physiologischer Größenordnung vollkommen unwirksam macht. Es erscheint wenig wahrscheinlich, daß der Effekt des Thiouracils auf zwei prinzipiell verschiedenen Mechanismen (Störung der Thyroxinsynthese in der Schilddrüse und Aufhebung der Thyroxinwirkung in anderen Geweben), beruht. Der Antagonismus Thiouracil: Thyroxin darf jedenfalls bei weiteren Untersuchungen über den Wirkungsmechanismus dieser und ähnlicher Stoffe nicht außer Betracht gelassen werden.

## Action of Podophyllin on the Number of Blood Leukocytes

It is well known that the action of caryoclastic DUSTIN[1] or mitotic LUDFORD[2] poisons on white blood-cells count. Colchicine brings about transient leukopenia followed by leukocytosis in the dog and the rabbit DIXON and MALDEN[3] and high leukocytosis in mice LITS[4]. Urethane produces strong diminution of the white blood-cells which counts in human leukemia, although in the normal human PATERSON *et al.*[5] and in the rabbit MOESCHLIN[6] the leukopenic effect is either inconstant or cannot be observed. The fact that podophyllin (KAPLAN[7]) as well as colchicine (KING and SULLIVAN[8]) inhibit cell proliferation in *Condylomata acuminata*, and normal skin suggested that podophyllin could induce modifications in the white blood-cells formation as colchicine does. As it is shown by the experiments reported below, this was actually the case.

White, normal, adult rats, of both sexes weighing 125–245 g, were injected with podophyllin intraperitoneally, first 0·25 mg, and later 0·50 mg each two or three days. The podophyllin was dissolved (0·50 mg/ml) in a 10% v/v ethanol-water mixture. Subcutaneous injections were discarded as a local necrosis was formed at the injection spot.

As reported in Tables I and II a marked diminution ranging between 38–42 p. c. in the number of white blood-cells was always found after the injection of a total dosis of 10·5 mg of podophyllin distributed over 60–75 days. The rats were apparently in good health, increased in weight and never had diarrhea. When distributed over a shorter time (40 days) the same amount of podophyllin produced a 50% leukopenia, but there appeared symptoms of poisoning, like diarrhea loss of weight, and finally death.

We are indebted to the Abbott Laboratories for a generous gift of the podophyllin employed.

*Table I*

| | Days after beginning of injections | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 8 | 20 | 36 | 48 | 60 | 75 |
| Rat No. 1 | | 9·4 | 9·1 | 9·1 | 9·0 | 7·5 | 5·4 |
| 2 | | 9·1 | 8·3 | 8·0 | 8·3 | 7·1 | 6·2 |
| 3 | | 9·6 | 9·6 | 9·0 | 7·8 | 6·2 | 6·1 |
| 4 | | 9·1 | 8·4 | 8·4 | 8·1 | 7·3 | 5·9 |
| Leukocytes × 1,000 (average) | 9·5 | 9·3 | 8·8 | 8·6 | 8·3 | 7·0 | 5·9 |
| Total podophyllin injected: 10·50 mg per rat | | | | | | | |

[1] A. P. DUSTIN, Le Sang *12*, 677 (1938).
[2] R. J. LUDFORD, Arch. Zellforsch *18*, 411 (1936), cit. by KING and SULLIVAN.
[3] W. E. DIXON and W. MALDEN, J. Physiol. *37*, 50 (1908).
[4] F. J. LITS, Arch. Int. Med. Expérim. *11*, 811 (1936).
[5] E. PATERSON, A. HADDOW, I. THOMAS, and J. M. WATKINSON, Lancet *250*, 677 (1946).
[6] S. MOESCHLIN, Exper. *3*, 195 (1947).
[7] I. W. KAPLAN, New Orleans Med. Surg. J. *94*, 388 (1942).
[8] L. S. KING and M. SULLIVAN, Science *104*, 244 (1946).

*Table II*

| | Days after beginning of injections | | | | |
|---|---|---|---|---|---|
| | 0 | 21 | 35 | 48 | 60 |
| Rat No. 1 | | 8·9 | 9·1 | 7·2 | 6·1 |
| 2 | | 9·3 | 8·0 | 6·9 | 5·3 |
| 3 | | 10·1 | 8·5 | 6·2 | 5·4 |
| 4 | | 10·2 | 9·3 | 7·1 | 6·1 |
| 5 | | 9·2 | 9·4 | 6·3 | 5·8 |
| Leukocytes × 1,000 (average) | 10·0 | 9·5 | 8·8 | 6·7 | 5·7 |
| Total podophyllin injected: 10·50 mg per rat | | | | | |

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*Zusammenfassung*

Wiederholte Injektionen von Podophyllin verursachen bei weißen Ratten eine Leukopenie. Gegenüber der Norm wird die Zahl der Leukozyten um ungefähr 40% vermindert.

## Influence de la concentration en calcium, potassium et magnésium du liquide céphalo-rachidien sur la consommation d'oxygène

Comme nous l'avons rapporté dans une communication antérieure[1] les modifications de la teneur en ions calcium, magnésium et potassium du liquide céphalorachidien exercent une influence considérable sur les mouvements respiratoires chez le chien, tant en ce qui concerne l'amplitude que la fréquence respiratoires. Ces observations, ainsi que celles de J. K. Merlis[2], de C. B. B. Downman et C. C. Mackenzie[3] et de C. B. Huggins et A. B. Hastings[4], qui avaient observé des modifications importantes du tonus musculaire après injection de ces divers ions dans le liquide céphalorachidien, nous ont amené à l'étude de la consommation d'oxygène sous l'influence des modifications de la concentration des ions calcium, potassium et magnésium dans le liquide céphalo-rachidien. Nos expériences ont été exécutées sur des chiens, anesthésiés à la morphine-chloralosane; pour déterminer la consommation d'oxygène, nous avons fait usage d'un appareil à métabolisme de Krogh. La perfusion des centres nerveux était assurée par une aiguille fixée à demeure dans un ventricule latéral permettant d'amener dans ce ventricule des solutions de compositions variées, préalablement chauffées à la température de l'animal; une seconde aiguille, placée dans l'espace sous-occipital, assurait l'écoulement de ce liquide de perfusion[5]. Voici brièvement les résultats obtenus:

1° L'installation de la perfusion des centres nerveux au moyen d'un liquide de base, contenant 0,139 g de chlorure de calcium, 0,246 g de chlorure de potassium et 0,114 g de chlorure de magnésium par litre, ne modifie nullement la consommation d'oxygène de l'animal.

2° Le passage du liquide de base à une solution riche en ions calcium (1 g $CaCl_2$ par litre) provoque une diminution d'environ 25% de la consommation d'oxygène.

3° Un liquide de perfusion privé de calcium détermine, par contre, une augmentation notable de la consommation d'oxygène (40% en moyenne).

4° L'excès de potassium dans le liquide de perfusion provoque également une augmentation considérable de la consommation d'oxygène, celle-ci atteignant en moyenne 35% pour une concentration de 1 g de chlorure de potassium par litre.

5° L'absence de potassium dans le liquide de perfusion ne donne lieu à aucune modification dans la consommation d'oxygène de l'animal.

6° L'augmentation des ions magnésium dans le liquide de perfusion détermine une diminution de la consommation d'oxygène, atteignant en moyenne 18% lorsque la concentration de chlorure de magnésium est portée à 1 g par litre.

7° Un liquide privé de magnésium ne provoque pas de changement notable dans la consommation d'oxygène.

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*Summary*

(1) The installation of the perfusion of the cerebral ventricles with a solution having nearly the same composition as the normal cerebrospinal fluid has no effect on the oxygen consumption of the animal.

(2) A solution with a calcium excess produces a decrease of the oxygen consumption.

(3) A perfusion with a calcium free solution increases the oxygen consumption.

(4) An excess of potassium in the solution which is used for the perfusion, increases also the oxygen consumption.

(5) A solution without potassium does not modify the oxygen consumption.

(6) An increase in the concentration of magnesium produces a decrease of the oxygen consumption of the animal.

(7) The absence of magnesium has no remarkable effect on the oxygen consumption.

## Das Eindringen von Sulfanilamid in die Lymphknoten

In den Arbeiten, die sich mit der Aufnahme und der Verteilung von Sulfonamiden in den Körpergeweben befassen[1], wurde das lymphatische System recht wenig beachtet. Um die chemotherapeutische Wirkung verstehen zu können, ist es indessen wichtig, zu wissen, in welchem Ausmaß diese Substanzen in die Lymphknoten eindringen.

Die im folgenden beschriebenen Versuche wurden mit Sulfanilamid als Modellstoff an 28 Kaninchen mit einem Durchschnittsgewicht von 2942 ± 62 g durchgeführt. Jedes Tier bekam mittels Schlundsonde eine einmalige Gabe von 0,25 g/kg; es wurde dann nach einer bestimmten Zeit (15 Min. bis 20 Stdn.) getötet. Die großen Knoten des intestinalen Lymphzentrums (Lymphonodi mesenterici) wurden herauspräpariert, gewogen, zerrieben und dreimal mit viel Wasser extrahiert. Das freie, chemotherapeutisch wirksame Sulfanil-

[1] J. M. Verstraeten, Arch. int. Pharmacodyn. *77*, 52 (1948).
[2] J. K. Merlis, Amer. J. Physiol. *131*, 67 (1940).
[3] C. B. B. Downman and C. C. Mackenzie, Lancet *2*, 471 (1943).
[4] C. B. Huggins and A. B. Hastings, Proc. Soc. Exper. Biol. and Med. *30*, 459 (1933).
[5] I. Leusen, Arch. int. Pharmacodyn. *75*, 422 (1948).

[1] Angaben siehe bei P. Egger, helv. med. acta, Ser. A, Suppl. XVII, Beilage zu Vol. 12, Fasc. *6* (1945).