

These findings corroborate GAILLARD's conclusion that the formation of 'colloid' and that of follicles in the embryonic thyroid are dissociated processes⁵. They suggest, moreover, that the thyrotropic and antithyroid agents can exert their respective effects on the embryonic gland *in vitro* already during the stage of histological differentiation. The agents used affected the formation of 'colloid' more markedly than that of follicles.

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Zusammenfassung

Schilddrüsenanlagen von Hühnerembryonen, in Ambion-Medium kultiviert, entwickeln sich schneller und zeigen beschleunigte intrafollikuläre Kolloidbildung. Mit Thiourazil behandelte Kulturen liessen retardierte Follikelbildung und Kolloidbildung erkennen.

The Organic Acid-Soluble Phosphate Contents of Mammalian and Avian Erythrocytes at the Beginning of Postnatal Life

In a previous communication¹ it has been pointed out that the organic acid-soluble phosphate (OAS-P) level in the erythrocytes of the newborn dog and rabbit is very low in comparison to that in the adult animal. This is a finding which is not at all in accord with observations reported by other investigators in various animal species. All the data in the literature available to us indicate that age and the OAS-P contents of the cellular elements correlate just the other way round. The red blood cells of the lamb², the calf³, and the young rat⁴, are richer in components containing OAS-P than the adults of these species. It is on this basis that GUEST and RAPOPORT⁵ regard the relatively higher organic phosphate level of the erythrocytes as characteristic of the young of all mammals. With a view to elucidating the prevailing contradictions our analyses were extended to numerous mammalian species and a number of domestic birds. The present paper incorporates the results obtained.

The organic phosphate fractions were determined from whole blood in the main according to BOMSKOV's method⁶. The corresponding phosphate levels of the red cells were calculated on basis of the hematocrit values. The so-called resistant fraction ($P_{\text{acid soluble}} - P_{180}$) contains the phosphoglycerate-phosphates of the blood. Except for the ruminants, in the red blood cells of the mammals the overwhelmingly greater part of the fraction consists of 2,3-diphosphoglycerate. Simultaneously with the working up of the blood of the newborns, determinations were in every case made from adult animals as well. Since the data we obtained for them agreed largely with the data in the literature, we were content to use a relatively small number of adults. Our findings, presented numerically in the attached Table, appear to permit the following conclusions.

The average values of OAS-P and resistant P in the erythrocytes of newborn and adult animals

Ordo	Species	Group ¹	Number of animals	OAS-P ($P_{\text{ac. sol.}}$ - $P_{\text{inorg.}}$)	Resist. P ($P_{\text{ac. sol.}}$ - P_{180})
				mg/100 ml cells	
Ungulata . . .	Horse	N	4	51.05	39.58
		A	3	51.87	42.17
	Pig	N	9	75.19	35.53
		A	5	102.62	72.30
	Cattle	N	5	42.98	27.30
		A	4	12.05	5.13
	Sheep	N	6	57.77	29.17
		A	3	20.87	3.47
Goat	N	2	58.85	33.25	
	A	2	15.33	6.20	
Carnivora . . .	Dog	N	14	34.71	13.03
		A	5	53.42	40.48
	Cat	N	10	19.16	10.00
		A	3	21.17	14.40
Rodentia . . .	Rabbit	N	20	42.68	16.68
		A	6	80.48	53.23
	Guinea pig	N	6	36.20	26.33
		A	3	49.30	36.20
Primates . . .	Man	N	3	48.30	30.90
		A	3	48.03	33.83
Rasores	Chicken	N	10	90.97	—
		A	3	95.73	—
	Turkey	N	4	119.75	—
		A	3	98.23	—
Lamellirostres .	Duck	N	3	108.43	—
		A	4	116.20	—

¹ N = Newborn, A = Adult

(1) From the point of view raised in the introduction, the mammals we studied can be divided into 3 groups. In 4 species (dog, rabbit, pig, and guinea pig), the red blood cells contain substantially less OAS-P in the newborn than in the adult animal. With the ruminants (cattle, sheep and goat) the situation is just the reverse: in relation to those of the adults, the erythrocytes of the newborns are remarkably rich in OAS-P. The rat too can be classed with this group. Finally, we have man, the dog and the cat, who show no appreciable differences in the two age groups.

The average values for domestic birds agree in the various age groups.

(2) The data in the Table show that from among the organic acid-soluble phosphate compounds, it is the phosphoglycerates (belonging to the resistant fraction), that are responsible for any differences, for the resistant P contents invariably change with the changes in the OAS-P level. Accordingly, in nucleated erythrocytes devoid of phosphoglycerate (avian), the OAS-P level is practically the same in the two age groups.

(3) As early as 1898, considerable differences were described by ABDERHALDEN⁷, in the phosphate contents of the blood of various mammalian species. Since the studies of RAPOPORT and GUEST⁸, the fraction which shows the widest quantitative differences by species, is known to be formed by the phosphoglycerates. Contrary to these conditions prevailing in adult animals, in the red cells of newborn mammals differences according to species of a substantially lower degree were only observed by us. Particularly striking is the great similarity of the resistant

¹ F. KUTAS and M. STÜTZEL, Acta vet. hung. 8, 1 (1958).
² A. I. MALAN, J. agric. Sci. 18, 397 (1928).
³ H. H. GREEN and E. H. MACASKILL, J. agric. Sci. 18, 384 (1928).
⁴ S. RAPOPORT and G. M. GUEST, J. biol. Chem. 126, 749 (1938).
⁵ G. M. GUEST and S. RAPOPORT, Phys. Rev. 21, 410 (1941).
⁶ C. BOMSKOV, Hoppe-Seylers Z. 210, 67 (1932).

⁷ E. ABDERHALDEN, Hoppe-Seylers Z. 25, 65 (1898).
⁸ S. RAPOPORT and G. M. GUEST, J. biol. Chem. 138, 269 (1941).

phosphate contents within the individual mammalian orders (Ungulata, Carnivora, Rodentia). In red blood cells produced in the earlier (foetal) ontogenetic stage the specific differences are assumedly even less distinct.

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Zusammenfassung

Die bisherigen Angaben eines reichen organischen säurelöslichen Phosphatgehalts der Erythrozyten können für junge Tiere nicht verallgemeinert werden.

Bei zahlreichen Säugerarten zeigen die Erythrocyten der Neugeborenen infolge einer sehr niedrigen Konzentration von Phosphoglycerinsäure einen Gehalt an organischem, säurelöslichem Phosphat, der unter demjenigen des ausgewachsenen Tieres liegt.

Wir stellen weiterhin fest, dass die bedeutenden Spezies-Unterschiede der Adulttiere in frühen Ontogenesephasen kaum hervortreten.

The Anti-Tumour Activity of 6-Azaauracil Riboside

It has recently been found in this Laboratory¹, and also independently by HANDSCHUMACHER and WELCH², that 6-azauracil inhibits the growth of a number of microorganisms. In the case of *Escherichia coli*, the inhibitory effect has a competitive character and may be cancelled by the addition of uracil, cytosine and uridine³. 6-Azaauracil has a marked inhibitory effect on a number of experimental cancer tumours⁴. It has been observed that when *Escherichia coli* is cultivated in the presence of 6-azauracil, some 6-azauracil riboside is formed; the formation of small amounts of the riboside has also been detected with *Streptococcus fecalis*⁵. Preliminary experiments have revealed pronounced cancerostatic effects of 6-azauracil riboside⁶; a detailed examination has not hitherto been possible due to lack of material.

More recently we have devised a method for the production of 6-azauracil riboside by a fermentation procedure which has made possible experiments *in vivo*⁷.

We first examined the effect of 6-azauracil riboside on Ehrlich's ascites tumours in subcutaneous form in white mice (strain H). Mice (weight 20 g) were subcutaneously inoculated with 0.2 ml of a diluted 8 days old ascites Ehrlich tumour (about 13×10^6 cells). Chemotherapy was

started on the fifth day following transplantation. The riboside was applied in physiological solution in 0.2 ml lots subcutaneously as far as possible from the tumour inocula. The daily dose of the drug given for 7 days amounted to 500, 250 and 50 mg pro 1 kg of weight of the test animal. 24 h after the last dose the tumours were taken out and weighed.

The results are given in the Table.

	Weight of tumor	P	Slowing down of growth of experimental tumour in %
Controls	348 ± 40.3		
500 mg azauracil riboside/kg	96.3 ± 11.5	< 0.01	72
Controls	559 ± 68.5		
250 mg azauracil riboside/kg	194.5 ± 21	< 0.01	65
50 mg azauracil riboside/kg	365.5 ± 52	0.037	35
* Controls	1169 ± 102		
500 mg azauracil/kg. . . .	890 ± 73	0.03	24

* The experiment with 6-azauracil is reported for comparison.

Our experiments show that in the 500 mg/kg dose 6-azauracil riboside is about 3 times more effective than 6-azauracil administered in the same concentration. When compared on a mole per mole basis, the riboside may be seen to be some 6 times more active than 6-azauracil itself. It should be noted, on the other hand, that 6-azauracil riboside has only a relatively weak inhibitory effect on the growth of *Escherichia coli*. It may be assumed that the mechanism of action of the two antimetabolites against tumour and microbial cells differs somewhat in character.

Dr. HÁVA and Mr. JANKŮ in the Pharmacological Laboratory of this Institute have found that the toxicity of 6-azauracil riboside, like that of 6-azauracil, is very low: a daily dose of 500 mg/kg, administered intraperitoneally for 8 days to white mice (strain H), had no adverse effects.

Clinical experiments with 6-azauracil riboside are now in progress.

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Zusammenfassung

Es wird die cancerostatische Wirkung des 6-Azaauracil-ribosids auf die subkutane Form des Ehrlich-Aszites-Tumors beschrieben und festgestellt, dass 6-Azaauracil-ribosid ungefähr 6mal wirksamer ist als 6-Azaauracil.

Die Hemmbarkeit der inhibitorischen Adrenalin- bzw. Noradrenalinwirkung durch Adrenolytika

Im Gegensatz zu den exzitatorischen Effekten des Adrenalins gelang die antagonistische Beeinflussung inhibitorischer Effekte durch Adrenolytika überzeugend nur am spontan arbeitenden Kaninchendarm. Für eine Gruppe dieser Substanzen, die β -Haloalkylamine, war der Nachweis eines Antagonismus bisher überhaupt nicht möglich.

¹ F. ŠORM and J. ŠKODA, Chem. listy 50, 827 (1956); Coll. Czechosl. chem. Comm. 21, 487 (1956).

² R. E. HANDSCHUMACHER and A. D. WELCH, Cancer Res. 16, 965 (1956).

³ J. ŠKODA and F. ŠORM, Chem. listy 50, 1165 (1956); Coll. Czechosl. chem. Comm. 21, 1328 (1956).

⁴ F. ŠORM, A. JAKUBOVIČ, and L. SLECHTA, Exper. 12, 271 (1956). T. M. HAKALA, L. W. LAW, and A. D. WELCH, Proc. Amer. Ass. Cancer Res. 2, 113 (1956). – J. ŠABLÍK and F. ŠORM, Neoplasma 4, 113 (1957). – H. KEILOVÁ and F. ŠORM, Neoplasma 4, 204 (1957).

⁵ J. ŠKODA, V. F. HESS, and F. ŠORM, Exper. 13, 150 (1957); Chem. listy 51, 1195 (1957); Coll. Czechosl. chem. Comm. 22, 1330 (1957).

⁶ J. ŠKODA and F. ŠORM, Chem. listy 50, 1165 (1956); Coll. Czechosl. chem. Comm. 21, 1328 (1956). – J. ŠKODA, V. F. HESS, and F. ŠORM, Exper. 13, 150 (1957); Chem. listy 51, 1195 (1957); Coll. Czechosl. chem. Comm. 22, 1330 (1957). – R. E. HANDSCHUMACHER, Biochim. biophys. Acta 23, 428 (1957). – R. SCHINDLER and A. D. WELCH, Proc. Amer. Ass. Cancer Res. 2 (3), 247 (1957).

⁷ J. ŠKODA and F. ŠORM, Biochim. biophys. Acta (in press).