pared to 55 for 200-kV. radiation[6], or a ten-fold difference in specific ionization. Sugiura[1], comparing gamma radiation with 200-kV. radiation, obtained a ratio of biological effectiveness of 0·67 for a seven-fold difference in specific ionization.

The results of this investigation will be published in detail elsewhere[7]. We are indebted to the National Cancer Institute of Canada and the Saskatchewan Cancer Society for generous support of our studies.

T. P. Ting
H. E. Johns
L. B. Jaques

Departments of Physiology and Physics,
University of Saskatchewan,
and the
Saskatchewan Cancer Commission,
Saskatoon, Sask.
April 2.

[1] Sugiura, K., *Amer. J. Cancer*, **37**, 445 (1939). Gray, L. H., and Read, J., *Brit. J. Rad.*, **21**, 5 (1948).
[2] Bliss, C. I., *Ann. App. Biol.*, **22**, 134 (1935).
[3] Ting, T. P., *Science*, **116**, 149 (1952).
[4] Ting, T. P., and Johns, H. E., *Rev. Can. de Biol.* (in the press).
[5] Ting, T. P., Johns, H. E., and Jaques, L. B., *Blood*, **7**, 826 (1952).
[6] Johns, H. E., *et al.*, *Amer. J. Roentgenol. and Rad. Ther.*, **62**, 257 (1949).
[7] Ting, T. P., and Johns, H. E., *Canad. J. Med. Sci.* (in the press).

## New Hydroxamic Acids as Antitubercular Agents

Previously, one of us suggested using salicylhydroxamic acid as an antitubercular agent[1]. The substance was subjected to clinical examination by another of us (S. H.) and showed promising results in fifteen cases of pulmonary tuberculosis. The substance was well tolerated by the patients, when large doses of 10–20 gm./day were administered.

This led one of us (T. U.) to look for more potent derivatives of salicylhydroxamic acid. Eventually, a number of derivatives of it were prepared. Some of them, for example, 3-bromosalicylhydroxamic acid ('*T* 40'), 2-hydroxy-3-methyl-benzhydroxamic acid (2,3-cresotinohydroxamic acid, '*T* 95'), 2-hydroxynaphtho-3-hydroxamic acid ('*T* 106'), 2-hydroxyquinoline-7-hydroxamic acid ('*T* 139'), proved to be more potent *in vitro* than salicylhydroxamic acid. All these substances are new to the literature.

5-Bromosalicylhydroxamic acid (m.p. 232°) was prepared by direct bromination of salicylhydroxamic acid in acetic acid medium and purified by crystallizing from alcohol[2]. 2,3-Cresotinohydroxamic acid (m.p. 148°–150° decomp.), 2-hydroxynaphtho-3-hydroxamic acid (m.p. 191°–192° decomp.) and 8-hydroxyquinoline-7-hydroxamic acid (m.p. 208°–209° decomp.) were prepared in the conventional way by the action of hydroxylamine on methyl esters of 3-cresotic, 2-hydroxy-3-naphthoic and 8-hydroxyquinoline-7-carboxylic acids respectively. Details of their preparation will be reported elsewhere[3].

The bacteriostatic concentration *in vitro* of these substances against saprophytic mycobacteria was found to be:

Table 1

| Sodium salts of | *T* 40 | *T* 95 | *T* 106 | *T* 139 | |
|---|---|---|---|---|---|
| | 15–30 | 15–75 | 8–16 | 2–4 | mgm. per 100 ml. |

Their toxicity to rats (lethal doses expressed in gm. per kgm. body-weight) is shown in Table 2.

Table 2. Lethal doses (gm./kgm. body-weight)

| Substance | *per os* | Subcutaneous | Intravenous |
|---|---|---|---|
| *T* 40 | *c.* 3·5 | 0·8 | 0·12 |
| *T* 95 | *c.* 3·0 | 0·6 | 0·15 |
| *T* 106 | *c.* 2·0 | (insoluble in water) | |
| *T* 139 | *c.* 2·0 | 0·3 | 0·03 |

Besides the toxicity control, the products have been examined as to their pharmacological activities on different organs. The experiments showed only a very weak action upon the animal organisms.

Experiments *in vivo* with '*T* 40' were carried out by using guinea pigs (*c.* 500 gm.) inoculated intraperitoneally with 0·1 mgm. of *Mycobacterium tuberculosis* ($H_{37}Rv$ strain). Administration of the drug started on the eighth day after inoculation and lasted for forty-two days. Thirty-five days later the animals were killed and the extent of tuberculous involvement was examined. The results are shown in Table 3.

Table 3

| Substance | No. of animals | Daily dose (mgm. per animal) | Administration | Mortality | Average tuberc. index | Average survival time |
|---|---|---|---|---|---|---|
| '*T* 40' | 20 | 10 | subcut. | 4 (20%) | 65 | 80·2 |
| Streptomycin | 20 | 10 | „ | 2 (10%) | 57 | 84·4 |
| Control | 20 | — | — | 18 (90%) | 100 | 47·2 |

Similar results were obtained with '*T* 106', the mortality being only slightly greater than that of the animals treated with streptomycin. The results with '*T* 95' were less favourable[4].

The action of bromosalicylhydroxamic acid on human tuberculosis was then investigated clinically. 1 gm. a day was administered in twenty-five cases for periods of 25–102 days; a total of 25–100 gm. was administered in each case. The drug was well tolerated even if the dose was increased to 2 gm. Particularly interesting were nine cases of tubercular meningitis, which did not appear to be influenced by streptomycin. The additional administration of '*T* 40' in most of these cases produced a considerable improvement. The results are shown in Table 4.

Table 4

| | After administration of '*T* 40'; number of cases | | | | |
|---|---|---|---|---|---|
| | Very great improvement | Considerable improvement | Marked improvement | No improvement | Worsening |
| Tubercular meningitis unsuccessfully treated with streptomycin | 1 | 4 | 2 | 1 | 1 |
| Miliary tuberculosis | | 1 | 2 | | |
| Infiltrative pulmonary tuberculosis | | 2 | 2 | 1 | 2 |
| Chronic cavernous tuberculosis | | | 1 | | 3 |
| Pleurisy with effusion and diffuse tuberculosis | 1 | | | | |

Of twenty patients showing radiologically tuberculous lesions in the lungs, nine showed a pronounced improvement of the radiological picture (two of them very considerable improvement), eight showed no improvement, and three became worse.

Some of the patients resistant to '*T* 40' have been treated with streptomycin; no improvement followed[5].

T. Urbański
S. Hornung
S. Slopek
J. Venulet

Department of Chemistry,
Institute of Technology,
Warsaw;
Institute of Tuberculosis,
Warsaw;
and Medical Academy,
Cracow.
June 2.

[1] Urbański, T., *Nature*, **166**, 267 (1950); *Gruzlica* (*Tuberculosis*), **18**, 206 (1950).
[2] Urbański, T., and Lewenstein, W., *Roczniki Chemii* (in the press).
[3] Urbański, T., Malinowski, S., Piotrowska, H., and Zakrzewski, L., *Roczniki Chemii* (in the press).
[4] Urbański, T., Serafinowa, B., Malinowski, S., Slopek, S., Kamieńska, I., Venulet, J., and Jakimowska, K., *Gruzlica* (*Tuberculosis*), **20**, 157 (1952).
[5] Hornung, S., and Krakowska, M., *Gruzlica* (*Tuberculosis*), **20**, 469 (1952).

## Survival of the Perfused Cat's Brain in the Absence of Glucose

In recent experiments in which the cat's brain was perfused through the isolated cerebral circulation with glucose-free 'simplified blood', brain functions were maintained for well over an hour if the rate of flow of blood was kept high. In previous perfusion experiments with glucose-free blood, the vascular resistance in the brain usually rose, reducing the rate of flow of blood considerably, with consequent loss of physiological activity of the brain and reduction of its oxygen consumption after 10–15 min. of glucose-free perfusion. When glucose was added afterwards to the blood, it was not taken up by the brain unless fresh liver extracts were also added[1].

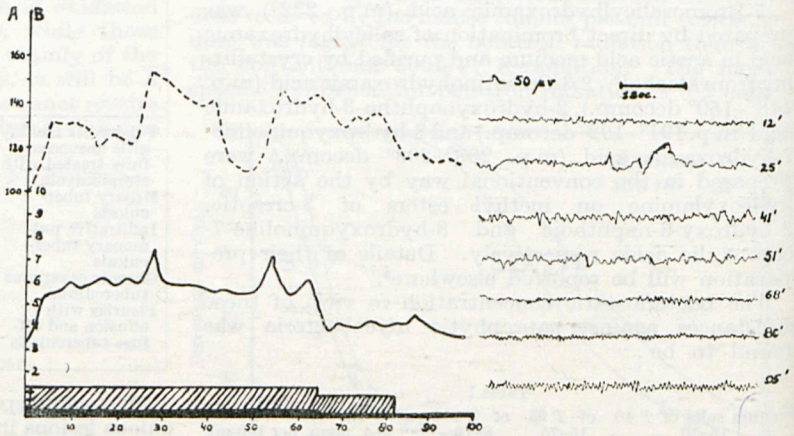
In the present experiments the technique of isolating the brain circulation and the method of perfusion were similar to that described previously[2]. Special care was taken to avoid contamination of the perfusion blood with the cat's systemic blood. Thiocyanate injected into the cat's circulation did not enter the perfusion blood. In some experiments all the extracranial soft tissue was removed from the head. These experiments gave results identical with those in which this precaution was not taken. Brain samples weighing 100–200 mgm. were excised during perfusion for analysis.

The bovine blood corpuscles used for perfusion were washed with 30–60 volumes of Ringer's solution containing penicillin, and 35 parts were suspended in 65 parts of a medium containing 7 per cent bovine serum albumin (Armour and Co.), 0·9 per cent sodium chloride, 0·044 per cent potassium chloride, 0·19 per cent sodium bicarbonate, 0·037 per cent calcium chloride, 0·038 per cent magnesium sulphate, and 0·021 per cent potassium dihydrogen phosphate. This 'simplified blood' was saturated with 5 per cent carbon dioxide in 95 per cent oxygen. A flow of 100–250 ml. per min. of blood for 100 gm. of brain was maintained.

*Brain activity.* A typical electro-corticogram is reproduced. In some experiments rhythmical electrical activity was still discernible after 90 min. of perfusion. The corneal reflex, respiration and vasomotor activity persisted for 60–100 min. The response to afferent stimulation of the sciatic nerve could be recorded from the cortex for a similar period of time. Addition of 'Metrazol' to the perfusion blood 40 min. after the start of perfusion caused convulsions which could be repeated; 3 mgm. of 'Nembutal' added to the perfusion blood at its entrance to the brain after 50–60 min. of perfusion extinguished the electro-corticogram within a few seconds and the corneal reflex and respiration shortly afterwards.

*Oxygen consumption.* During the present glucose-free perfusion experiments, oxygen consumption was very nearly as high as in other experiments in which glucose was present in the 'simplified blood'[3]. The usual rates were 5–7 ml. oxygen per 100 gm. brain per min. The total amount of oxygen consumed by the brain during the first hour of glucose-free perfusion exceeded by several times the amount necessary for the oxidation of the carbohydrates available at the start of the perfusion in the brain. During metrazol convulsions, even when 'Metrazol' was administered 50–60 min. after the start of glucose-free perfusion, the rate of oxygen consumption increased two- to three-fold. 'Nembutal' in a concentration of 3 mgm. in 100 ml. blood decreased the oxygen consumption only slightly. The respiratory quotient of the brain was 1·00 at the outset and decreased as perfusion progressed. Values as low as 0·50 were found frequently, even though the oxygen consumption remained high.

The glucose content of the brain was usually very low or dropped to zero after 10 min. of perfusion. In most experiments a small amount of glycogen remained in the brain throughout. A slight increase of glycogen in the brain was also found in some cases towards the end of the perfusion period. The concentration of lactic acid in the brain decreased gradually during perfusion, contrasting in this respect with similar experiments in which the perfusion blood contained glucose[3]. The potassium concentration in the brain decreased gradually and the sodium concentration increased during perfusion. Thus in some cases during prolonged perfusion experiments while




Typical glucose-free perfusion experiment. Ordinate: *A*, blood flow; *B*, oxygen consumption, ml. per 100 gm. of brain per min. Abscissa: perfusion time in minutes. Shaded area, corneal reflex; heavy line on abscissa, duration of natural respiration. Full line, oxygen consumption; broken line, rate of flow of blood. The figures next to the electrocorticograms show perfusion times in minutes