cœur. Le bouton a un diamètre presque double de celui de sa fibre. Il est à peu près sphérique et un peu moins coloré que cette dernière.

On voit dans la fig. 2 une fibre un peu plus petite que la précédente. Elle se divise en deux branches: l'une se termine par un anneau; l'autre est coupée par le rasoir. Non loin de là, une fibre plus fine aboutit également à un petit anneau dans la profondeur de l'épinèvre.

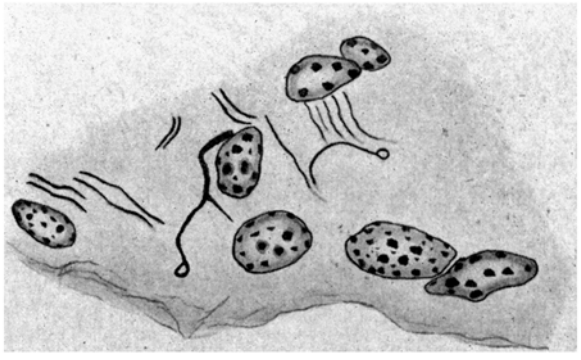

Fig. 2.

La fig. 3 présente une fibre nerveuse noire et très fine, comparable à une fibre postganglionnaire parasympathique. Elle se termine par un appareil métaterminal de quelques petits grains à la surface d'une cellule du tissu conjonctif de l'épinèvre. La continuation de ces grains avec la fibre est très évidente et la limite de cette terminaison est très précise. Dans un travail ultérieur, j'exposerai les différences d'aspect que présentent les fibres nerveuses cardiaques suivant leur origine ou leur fonction. Dès à présent je puis dire que les fibres abou-

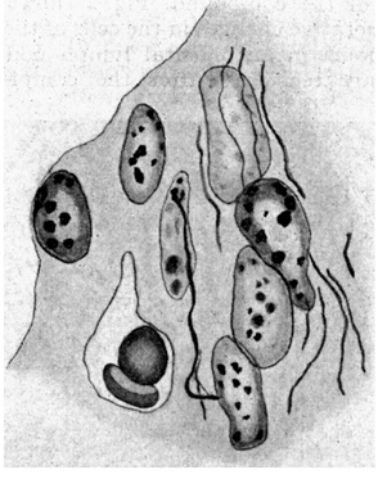

Fig. 3.

tissant à des terminaisons comme celles des fig. 1 et 2, ont l'aspect et la coloration de fibres sensitives. Il est donc vraisemblable qu'elles viennent des nerfs vagues, puisque ce sont eux qui fournissent les voies afférentes du cœur. En ce qui concerne la terminaison de la fig. 3, en raison de l'aspect différent de la fibre qui lui donne naissance, il est possible qu'il y ait là un appareil en rapport avec une fonction trophique.

J'ai vu aussi des fibres ténues accompagnant des fibres encore plus fines et colorées en jaune, dans l'épinèvre tout près d'un vaisseau. Il est bien possible que ce soient des fibres vasomotrices du système végétatif.

En résumé, dans l'épinèvre des gros nerfs du cœur chez le Chat nouveau-né, on trouve des fibres sensitives qui se terminent d'une manière différente soit par des boutons, soit par des anneaux, ou bien par un appareil métaterminal. Quelques-unes de ces fibres appartiennent peut-être au système nerveux autonome. Des fibres vaso-motrices ont été aussi trouvées dans l'épinèvre comme dans d'autres organes. K. T. TCHENG

Laboratoire de neuro-histologie, Institut d'anatomie de l'Université de Genève, le 2 mai 1949.

Summary

The cardiac nerves which are composed of a mixture of sympathetic and parasympathetic motor fibres, also comprise sensorial fibres that belong exclusively to the parasympathetic system. A certain number of these afferent fibres ends in the epineurium of the nerves in different forms:— enlargements, terminal rings, or metaterminal apparatus of WEBER.

Histological Changes Produced by Large Doses of Tetra-sodium 2-methyl-1:4-naphthohydroquinone Diphosphate in some Human Tumours

Clinical trials of large doses of tetra-sodium 2-methyl-1:4-naphthohydroquinone diphosphate, mainly in conjunction with palliative X-ray therapy in patients with various types of advanced malignant tumours have been in progress since November 1946. The results in 116 cases have been reported[1]. It has been found that the compound in large doses produces a small but useful improvement in the palliative results of X-ray therapy in some cases of advanced cancer, and a small increase in survival time in cases of inoperable carcinoma of the bronchus. The compound is already in use in medicine as a water-soluble synthetic vitamin-K substitute. It is of low toxicity, and has been administered by intramuscular and preferably intravenous injection. It is of interest that large intravenous doses produce almost immediate focal pain in the region of the tumour in some cases, especially where there is bone involvement. This focal pain appears to be due to temporary cell œdema.

This approach to the problem of attempting to improve the treatment of cancer by the combined use of radiotherapy and chemotherapeutic agents was based on the finding that therapeutic doses of ionizing radiations produce a disturbance of cellular nucleic acid metabolism including inhibition of synthesis of thymonucleic acid in proliferating cells[2].

It has been shown[3] that the compound produces mitotic inhibition in chick fibroblast cultures and in some human squamous cell carcinomata, and that in the tissue cultures, significant potentiation of the effects of X-radiation and the compound in inhibiting mitosis was found under suitable conditions.

[1] J. S. MITCHELL, Brit. J. Cancer *2*, 351 (1948).

[2] J. S. MITCHELL, Nature *146*, 272 (1940); Brit. J. Exp. Path. *23*, 285, 296, 309 (1942); Brit. J. Radiol. *16*, 339 (1943); 21st Ann. Rep. Brit. Emp. Cancer Campaign 62 (1944); Schweiz. med. Wschr. *76*, 883 (1946). – H. v. EULER and G. HEVESY, Kgl. Danske Vidensk. Selskab Biol. Medd. *17*, 8 (1942). – L. AHLSTRÖM, H. v. EULER and G. HEVESY, K. Svensky Vetenskaps Akad. Ark. Kemi 19A. No. 9 (1944). – G. HEVESY, Rev. Mod. Physics *17*, 102 (1945). – R. E. STOWELL, Cancer Res. *5*, 169 (1945). – B. E. HOLMES, Brit. J. Radiol. *20*, 450 (1947). – J. O. ELY and M. H. ROSS, Cancer Res. *8*, 285 (1948).

[3] J. S. MITCHELL and I. SIMON-REUSS, Nature *160*, 98 (1947).

The antimitotic action of quinones is well known[1]. The mutagenic effect of phenol in *Drosophila*[2] and chromosome fragmentation induced by phenols[3] is of interest. The parallelism between mitotic inhibition and interaction with –SH compounds *in vitro* has been studied[4]; it is unlikely that this is the only mechanism involved, but it is of interest in relation to the radiosensitivity of some –SH enzymes[5].

The purpose of this note is to present histological confirmation of the late effects of repeated large doses of the compound in some human tumours other than the squamous cell carcinomata previously exemplified[6].

Fig. 1 (*a* and *b*) show the histological findings in biopsy specimens from the case of a man aged 82 years, with an advanced carcinoma of the skin, originally of basal cell type, involving the right side of the nose with gross destruction of the tissues of the face, including bone. There were no secondary glands. This lesion had become radio-resistant and had recurred after much previous treatment over many years. The original treatment was by diathermy, and subsequent radium. Two courses of radical X-ray treatment had been given for recurrences, and further palliative X-ray treatment had been attempted without any response. Fig. 1*a* is

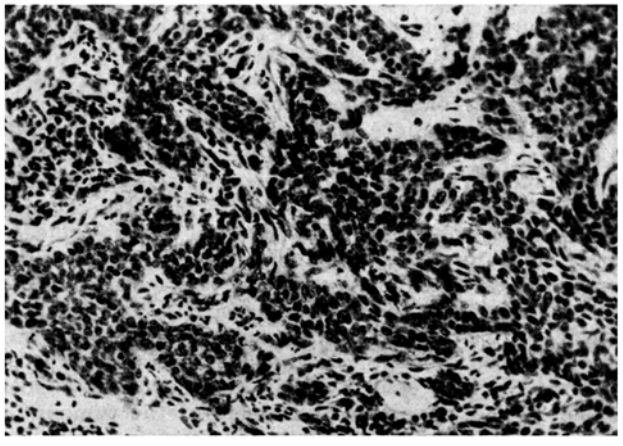

Fig. 1*a*

from the biopsy specimen before a final course of radical X-ray therapy combined with intramuscular injections of the compound. The second biopsy shown in Fig. 1*b* was taken three days after 4,500 r of X-radiation in 21 days, and immediately after the last of 26 daily intramuscular injections, each of 100 mg of the compound. The immediate clinical response of the lesion to the traatment was surprisingly good, but active though slowly progressive malignancy was still present after nine months. In the second biopsy, the field shown in Fig. 1*b*, was the only part of the section containing tumour cells, which it is interesting to note are of degenerating squamous cell type, with keratinization. The lesion apparently became radio-sensitive again with the combined use of the compound and X-radiation.

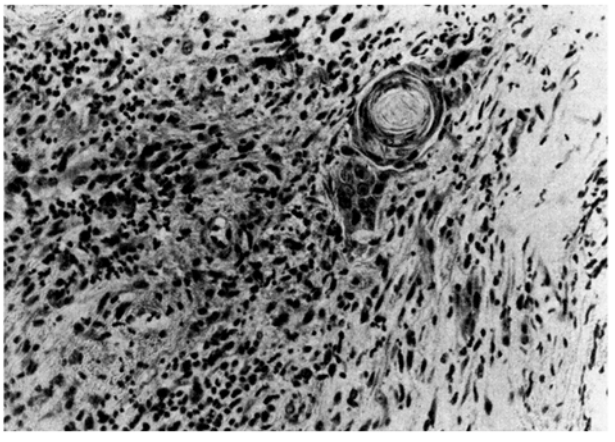

Fig. 1*b*

Fig. 2 shows the effects of the compound alone in the case of a man aged 52 years suffering from an adenocarcinoma of the transverse colon with secondary involvement of lymph nodes in the omentum, and also in the left supraclavicular area and posterior triangle. After failure of the cervical nodes to respond to palliative X-ray therapy, clinical retrogression of all the palpable nodes occurred after intravenous administration of large doses of the compound. Fig. 2 shows the widespread degenerative changes in the cells of the secondary adeno-carcinoma in an omental lymph node removed at laparotomy ten days after the completion of a

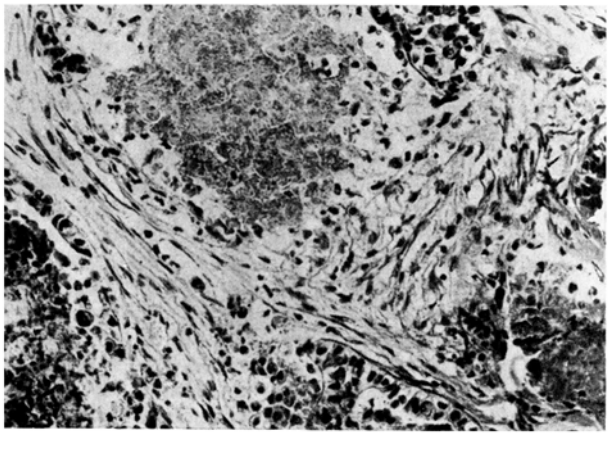

Fig. 2.

course of daily injections of the compound, during which a total dose of 8,140 mg was given in 31 days. No X-radiation had been given to this area at any time. As in the cervical nodes, the tumour shows necrosis and gross degeneration, with an increase of fibrotic stroma. There are no mitoses, and practically all the recognizable tumour cells show pyknotic nuclear degeneration. It is emphasized that the therapeutic effect was only pal-

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[2] E. HADORN and H. NIGGLI, Nature *157*, 162 (1946).

[3] A. LEVAN and J. H. TJIO, Hereditas *34*, 250 (1948); ib. *34*, 453 (1948). – R. PARMENTIER and P. DUSTIN, Nature *161*, 527 (1948).

[4] E. FRIEDMANN, D. H. MARRIAN, and I. SIMON-REUSS, Brit. J. Pharmacol. *3*, 265 (1948); ib. *3*, 335 (1948).

[5] E. S. G. BARRON, MDDC – 484. U.S.A.E.C. Rep. (1946) (Lecture at University of San Marcos, Lima).

[6] J. S. MITCHELL and I. SIMON-REUSS, l. c.

liative, the patient dying at 14 weeks after the beginning of the course of injections.

No histological evidence of toxic effects on any normal organs and tissues attributable to the compound has been found. The earlier cytological changes produced by the compound alone will be reported elsewhere. Probably the first change is temporary cell œdema, but the most obvious change is mitotic inhibition, with cytoplasmic and nuclear enlargement in some cells, and formation of bi- and multinucleate cells, with large nucleoli and chromo-centres. Although with the high concentrations used, chromosome stickiness and nuclear pyknosis are produced, appearances suggesting fragmentation of chromosomes can almost always be found. Anaphase bridges are only rarely produced by the compound alone, unlike X-rays.

Acknowledgements. The preparation of the compound used was "Synkavit" manufactured by Roche Products Ltd., of Welwyn Garden City. I wish to thank Dr. F. WRIGLEY for supplies of the compound.

I wish to thank Mr. E. W. MITCHELL for his skilled technical help in the preparation of the photomicrographs, and Dr. A. M. BARRETT, of the University Department of Pathology, for the sections.

J. S. MITCHELL

Department of Radiotherapeutics, University of Cambridge, April 5, 1949.

Summary

Un certain nombre de malades atteints de diverses tumeurs malignes avancées ont été traités avec de fortes doses de tétra-sodium-2-méthyl-1,4-naphtohydroquinone diphosphate, traitement combiné dans la plupart des cas à une thérapie palliative par les rayons X.

Les expériences histologiques confirment la réponse positive, obtenue par l'action des rayons X combinés à celle de la substance en question, dans un cas avancé de carcinome de la peau faciale, auparavant réfractaire au traitement par les rayons X. En outre, dans un cas de métastases de nœuds lymphatiques d'un adénocarcinome primaire du colon, les documents histologiques montrent la régression et la dégénérescence des cellules de la tumeur, effets exclusivement attribuables à la substance appliquée.

Der Übertritt von Fluorescein aus dem Blut ins Kammerwasser des normalen Menschen

Das Problem, ob Kammerwasser durch das Auge strömt oder ob nur ein Diffusionsaustausch zwischen Blut und Kammerwasser stattfindet, ist heute durch die Entdeckung der Kammerwasservenen beim Menschen[1] im Sinne der Strömung entschieden. Die nächsten Fragen, die sich aufdrängen, sind: 1. Wird das Kammerwasser des Menschen durch einen sekretorischen oder nur durch einen Filtrationsprozeß geliefert, und 2. wie groß ist die Durchflußmenge pro Minute?

Mit einem besonderen Spaltlampenfluorometer das wir andernorts beschrieben haben[2], wurde der Verlauf des Kammerwassergehalts an Fluorescein in 10 normalen Augen verfolgt, nachdem die Versuchspersonen 4 cm³ 10%iger Fluorescein/Natrium-Lösung intravenös erhalten hatten. Die Fluoresceinkonzentration der Vorderkammer wurde mit dem Ablauf der Konzentrationsänderung des Blutultrafiltrats verglichen. Es ergibt sich (Tabelle, Stab 6), daß regelmäßig die maximale Konzentration des Fluoresceins in der Vorderkammer eine Zehnerpotenz niedriger ist als das gleichzeitige Konzentration des freien Fluoresceins im Blute. Wasser tritt also beim normalen Menschen fluoresceinärmer in die Vorderkammer ein, als das Ultrafiltrat des Blutes ist. Der Vorgang der Kammerwasserbildung kann also keine Ultrafiltration sein.

Ausgehend von der bewiesenen Strömung des Kammerwassers ergibt die mathematische Analyse, daß, von der 20. bis zu der 25. Minute nach der intravenösen Fluoresceininjektion angefangen, der folgende Differentialansatz gültig ist:

$$\frac{dc_v}{dt} = (k_1+k_2)\, c_{Bl} - (k_1+v)\, c_v$$

Darin bedeutet c_v Konzentration des Fluoresceins in der Vorderkammer, c_{Bl} die gleichzeitige Blutkonzentration an freiem (ultrafiltrablem) Fluorescein. k_1 ist eine Konstante, die der Diffusion des Fluoresceins in und aus der Vorderkammer durch die Irisvorderfläche zugeordnet ist, k_2 eine Konstante, die den Eintritt des Fluoresceins aus der Hinterkammer in die Vorderkammer charakterisiert. v ist der Bruchteil des Vorderkammervolumens, der pro Minute durch Strömung ersetzt wird, wenn die Zeit in Minuten gerechnet wird. k_1, k_2 und v haben gleiche Dimension. $(k_1 + k_2)$ charakterisiert also den Eintritt von Fluorescein in die Vorderkammer, $(k_1 + v)$ seinen Austritt. $100 \cdot v$ ist das prozentuale Minutenvolumen der Vorderkammer. k_1 ist gegenüber v sehr klein, so daß $v \sim k_1 + v$ ist. Aus der Integration der obigen Formel läßt sich $k_1 + v$ bestimmen. Die Tabelle zeigt

1	2	3	4	5	6	7	8	9
Nr.	Name	Alter	Auge	Tension in mm Hg	$\frac{C_v\ max}{C_{Bl}}$	$k_1 + v$	V in mm³	v in mm³
1	D. Fred	32	o.d.	15	0,079	0,012	208	2,5
2	St. Max	37	o.d.	18	0,08	0,012	179	2,1
3	W. Hans	28	o.d.	17	0,082	0,012	197	2,3
4	R. Karl	29	o.d.	19	0,098	0,014	150	2,1
5	Sch. Herta	25	o.d.	21	0,067	0,01	186	1,9
6	E. Verena	19	o.d.	12	0,07	0,01	187	1,9
7	K. Hanna	21	o.d.	23	0,098	0,009	170	1,5
8	D. Gottlieb	61	o.d.		0,112	0,014		
9	B. Emma	67	o.d.	20	0,115	0,008	137	1,1
10	Ae. Rudolf	41	o.d.	16	0,16	0,008	216	1,7
					0,096	0,011 ± 0,0022		1,9

Stab 5: Augendruck in mm Hg, nicht am Tage des Versuches bestimmt.

Stab 6: Verhältnis der Fluoresceinkonzentration im Kammerwasser zur Konzentration des freien Fluoresceins im Blut zur Zeit der maximalen Konzentration in der Vorderkammer. Versuchsperson 9 und 10 litten am nichtuntersuchten Auge an einer Iridozyklitis.

Stab 7: Siehe Text.

Stab 8: Volumen der Vorderkammer.

Stab 9: Kammerwasser-Minutenvolumen in mm³.

(Stab 7), daß das prozentuale Minutenvolumen des normalen Menschen 1,1% des Kammerinhalts ist. Bestimmt man in jedem Falle das Volumen der Vorderkammer[1] (Stab 8), so erhält man das Minutenvolumen der menschlichen Vorderkammer in mm³ zu rund 2 mm³ pro Minute (Stab 9).

Eine ausführliche Mitteilung dieser Versuche erfolgt in der Zeitschrift «Ophthalmologica».

H. GOLDMANN

Universitätsaugenklinik, Bern, den 28. April 1949.

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