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Editorial

Las investigaciones realizadas en las últimas décadas sobre los tumores del cerebro han permitido progresos fundamentales conducidos en distintas direcciones.

Diversos aspectos de su biología; su detección y tratamiento, han sido los lineamientos generales de más interés en la orientación de los estudios.

La biología de los tumores cerebrales, su génesis a partir de varios tipos de células del C.N.S., la producción experimental y su transplante, los aportes de la microscopía electrónica, de la histoquímica, los cultivos de tejidos, plantean una problemática interesante con respecto a cómo pueden originarse y qué agentes podrían estar en juego, y a qué criterio ceñirse para llegar a una clasificación práctica aceptable para todos.

Los procedimientos para detectar el tumor se han multiplicado y se trata de definir en qué casos cada uno da sus mejores resultados. Por las características de la clínica neurológica interesa saber no sólo si existe un tumor, sino que también es un asunto primordial determinar con la mayor precisión dónde está situado.

En ningún capítulo de la medicina el principio de localización tiene tanta importancia como en la clínica neurológica.

Antes del advenimiento de las técnicas complementarias para el estudio de los tumores, diagnosticar su existencia al comienzo de su evolución y precisar en qué lugar se encontraba, significaba a menudo para el médico un problema difícil y la confirmación de su diagnóstico constituía motivo de gran satisfacción y orgullo.

Desde que Dandy en 1918 creó la técnica de la radiografía cerebral constrastada con aire, este diagnóstico se hizo mucho más fácil y dejó de ser por lo general una hazaña clínica.

Posteriormente se agregaron otras técnicas de examen: la angiografía, la electroencefalografía, la gammaencefalografía, la rheoencefalografía y la ecoencefalografía.

Los progresos y las facilidades para el diagnóstico han corrido a la par con los adelantos en los métodos de tratamiento.

Debemos subrayar sin embargo que el buen examen clínico y su correcta interpretación siguen teniendo plena vigencia, puesto que los estudios complementarios muy a menudo sólo adquieren su pleno valor cuando luego de ser analizados se les integra con los datos obtenidos por la clínica.

El tratamiento tiene hasta ahora sus perspectivas condicionadas principalmente a la naturaleza y sitio del tumor. La cirugía, la roentgenterapia, la aplicación directa de radioisótopos, los agentes químicos, traducen esfuerzos renovados en la lucha contra esta terrible enfermedad.

En la realización de este número dedicado a los Tumores del Cerebro, hemos tenido la fortuna de vernos honrados con las importantes colaboraciones de los Dres. F. Ikuta y H. M. Zimmerman; D. Gordon Potts; W. H. Oldendorf; G. Ruggiero; O. Magnus y J. H. A. van der Drift; J. Talairach, G. Szikla, A. Bonis, J. Bancaud y C. Schaub; J. Hankinson; B. Woodhall y M. S. Mahaley; Harold C. Voris, Brian Baldwin, a quienes agradecemos en nombre de los Editores por los valiosos trabajos que nos han permitido ofrecer a nuestros lectores.

VICTOR SORIANO.

The Viral Particles in the Reactive Cells of the Brain Induced by Chemical Carcinogens

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Over a half century ago the concept of a viral etiology in neoplasia was elaborated by Rous[17]. Since that time, a great number of observations on this subject have been published by many investigators. Among them should be mentioned the observations of Shope[18] on the papilloma virus, Bittner[3] on the milk agent in mammary carcinoma of the mouse, Gross[9] and Stewart et al.[20] on the polyoma virus, and Maloney[15] on the leukemia virus. Recent technical advances, especially in tissue culture and the use of the electron microscope, have spurred a new interest in this subject.

Simultaneously with these investigations, many observers concentrated on the role which various carcinogenic chemical compounds play in tumor production. This followed the first successful attempt in carcinogenesis by Yamagiwa and Ichikawa[21], who applied coal tar to the rabbit's ear and produced cancer.

Thus, in the field of experimental cancer research both a virus and a chemical carcinogen have been implicated, but each has been investigated independently of the other. No definite correlations have as yet been made between the modes of action in tumorigenesis of these two groups of agents.

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Fig. 1. — Slice of C3H mouse brain implanted with pellet of methylcholanthrene 3 months previously. Arrow points to pellet.

Fig. 2. — Light microscopic appearance of lesion on margin of pellet, between which and adjacent brain tissue (B) many reactive cells and numerous empty spaces (M) may be seen. The latter represent dissolved out carcinogen (methylcholanthrene). Vestopal embedding; Bielschowsky's silver impregnation; x400.

Fig. 3. — Fragmented methylcholanthrene crystals (M) appear as empty spaces in cytoplasm of reactive cells. These intermingle with glial fibers (gf). Most empty spaces are lined by "saw-tooth" margins. x10,000.

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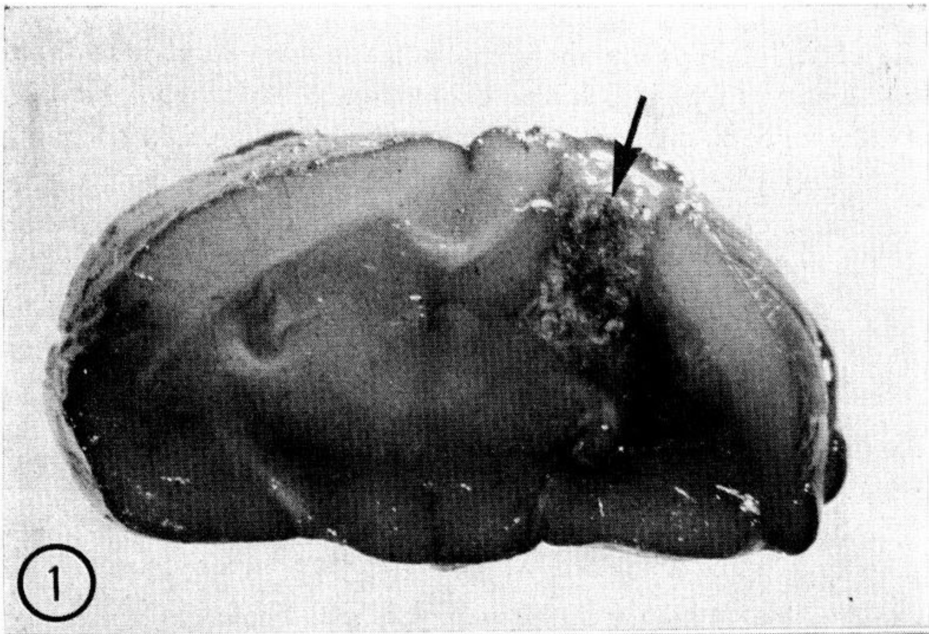
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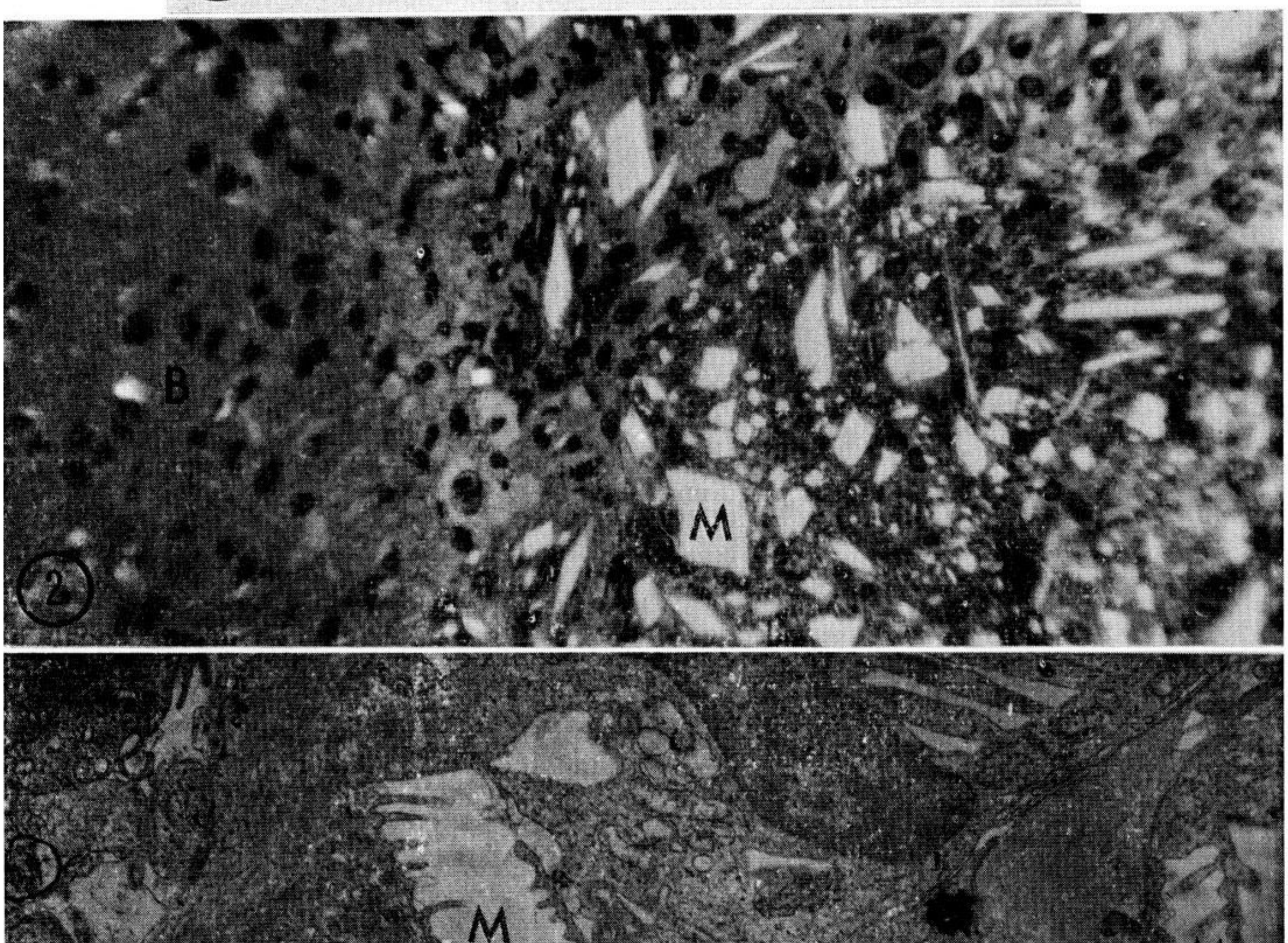
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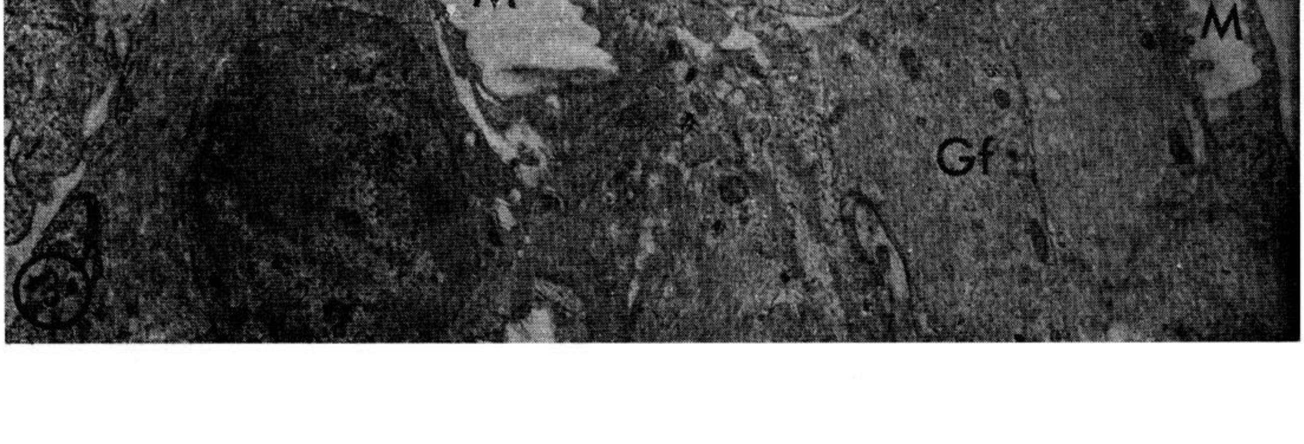
M
M
Gf
3

Since 1941, one of us (HMZ) has been engaged in the production of various kinds of cerebral and other neoplasms by the intracerebral and extracranial implantation of a variety of chemical carcinogens. Both the tumors and the precancerous lesions thus induced have been studied extensively [1, 22, 23, 24, 25, 26]. Recently, these studies have been extended to include electron microscopic observations of the brains of C3H mice which were previously implanted with pellets of 1, 2, 5, 6-dibenzanthracene[11]. The brains were examined at intervals up to two years following implantation of the carcinogen. During this study it became apparent that particles of cylindrical or filamentous form, but of unknown nature, were present in the reactive cells adjacent to or containing fragmented crystals of the carcinogen. These RNA particles were noted during the time interval of the precancerous stage of the lesion. They seemed to multiply in number and were observed in case after case. This was also true in the extracranial lesions produced with carcinogen[12]. No particles were noted in lesions produced by non-carcinogenic materials[11].

This report will deal with the cylindrical, filamentous particles which developed in the intracranial reaction induced by the implantation of methylcholanthrene and benzpyrene.

MATERIALS AND METHODS

The animals utilized in this investigation were C3H mice, pan-bred in the animal quarters of Montefiore Hospital, from an original colony supplied by Dr. Leonel Strong of the Yale University School of Medicine in 1948.

Intracerebral implantations of pellets of 20-methylcholanthrene (Hoffman - La Roche, Inc., Nutley, N. J.) were made into four female mice at seven weeks of age. Two animals were sacrificed after two months and the remaining two were examined three months later. Another group of 11 male and female mice were implanted intracerebrally with pellets of 3,4-benzpyrene (Meurice, Union Chimique Belge, Brussels, Belgium). These animals were between five and nine weeks of age at the start of the experiment. Two females of this group were sacrificed at two months after implantation; five male mice were examined three months later; the remaining four males were examined nine months after the start of the experiment. The preparation of the pellets of carcinogens, operative procedures, anesthesia, animal care, and diet were all similar to those previously employed in experiments with methylcholanthrene[22] and benzpyrene[23].

Electron and light microscopic preparations were made in each instance from the cerebral tissues obtained by craniotomy while the animals were still living. Portions of the brains containing the pellets were sliced immediately in a coronal fashion at about 2 mm in thickness within buffered osmium tetroxide at pH of. 7,4 and at 0°C to 4°C (Fig. 1). Twenty mi-

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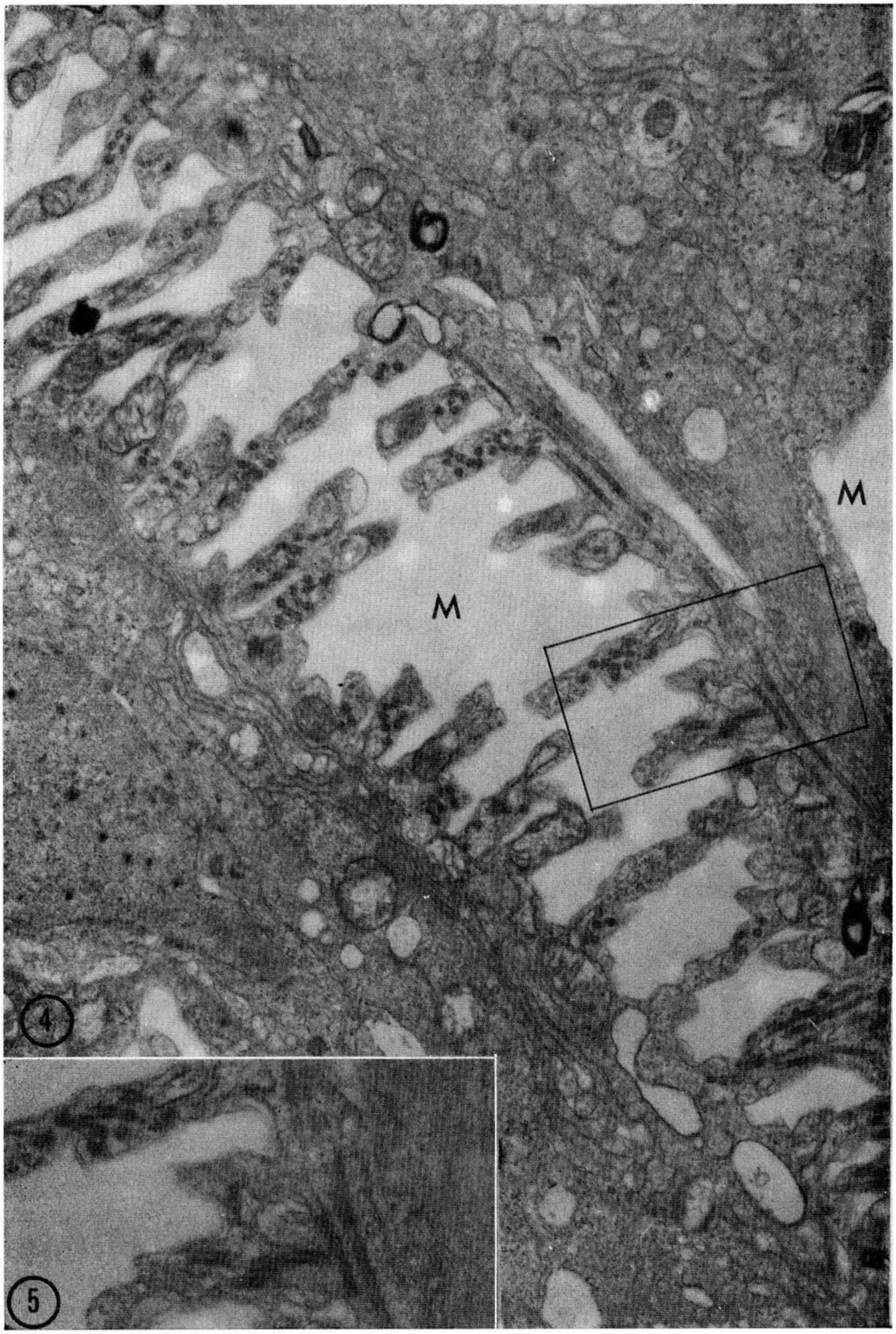
Fig. 4. — Methylcholanthrene crystal space (M) bordered by reactive cell cytoplasm containing cylindrical electron-dense particles. x21,500.

Fig. 5. — The oblong field in figure 4 is shown under higher magnification in figure 5. Particles in longitudinal view are seen near the carcinogen. x35,000.


M
M
4
5

nutes later, five to seven blocks of tissue, each about 1 cmm in diameter, containing the pellet and adjacent cerebral parenchyma were removed from the brain slices under a dissecting microscope and fixed further in osmium tetroxide for 100 minutes. They were then dehydrated in increasing concentrations of ethanol and transferred into acetone. Following two changes of fresh acetone at 15 minute intervals, the blocks were embedded in vestopal. The remainder of the brain slices were in the meantime fixed in 10 per cent formalin for paraffin embedding and study with the light microscope. Thick sections of the vestopal-embedded blocks were also prepared for light microscopic examination and. These were stained with toluidine blue and with Bielschowsky's silver impregnation (Figs. 2, 12 and 16). Ultra-thin sections for electron microscopy were prepared from these blocks containing the carcinogens. The sections were stained usually with lead hydroxide for seven minutes according to the method of Millonig[14], or were stained with uranyl acetate. In some instances they were left unstained. The electron microscope employed was an RCA EMU 3D.

OBSERVATIONS

Methylcholanthrene

The implanted pellets of carcinogen were present in the frontal, parietal or occipital lobes, with extension of the surrounding reaction to the lateral (Fig. 1) or third ventricles. Under the light microscope, the sites of the pellets were observed as large empty spaces, but between them and the adjacent tisssue there were numerous smaller empty spaces within or between reactive cells. These empty spaces had resulted from the solution of the methylcholanthrene by ethanol and acetone during tissue dehydration (Fig. 2). Some of the empty spaces had ragged walls with an appearance not unlike saw teeth.

In electron micrographs the methylcholanthrene crystal spaces also appeared as clear, unstained cavities with ragged, sawtooth walls (Figs. 3, 4, 5 and 6). These empty spaces were noted both within the cytoplasmic matrix of the reactive cells and between these cells. At the stages of the reactive response which were examined, some of the cells resembled glia while others appeared to be altered leukocytes. It was not possible, however, to identify with certainty every reactive cell. Many had numerous pseudopodia (Fig. 11) which intermingled with definite glial cell processes (Fig. 3).

Within the cytoplasmic matrix surrounding the crystals, numerous electron-dense particles were noted (Figs. 4, 5, 6 and 7). These were strongly osmophilic and had no characteristic arrangement, although they always appeared in multitudes. These particles were found in one of the two mice examined two months after pellet

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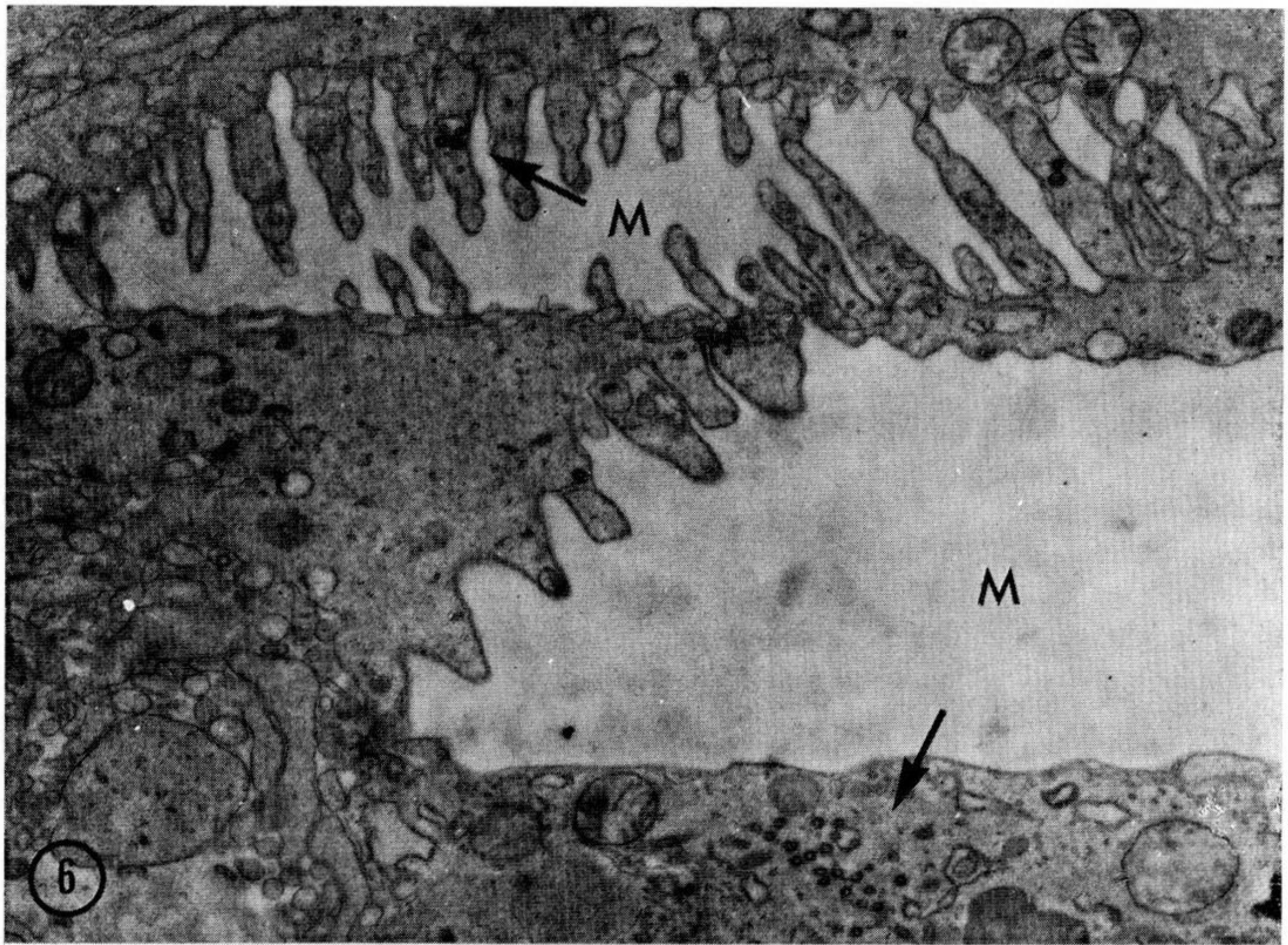
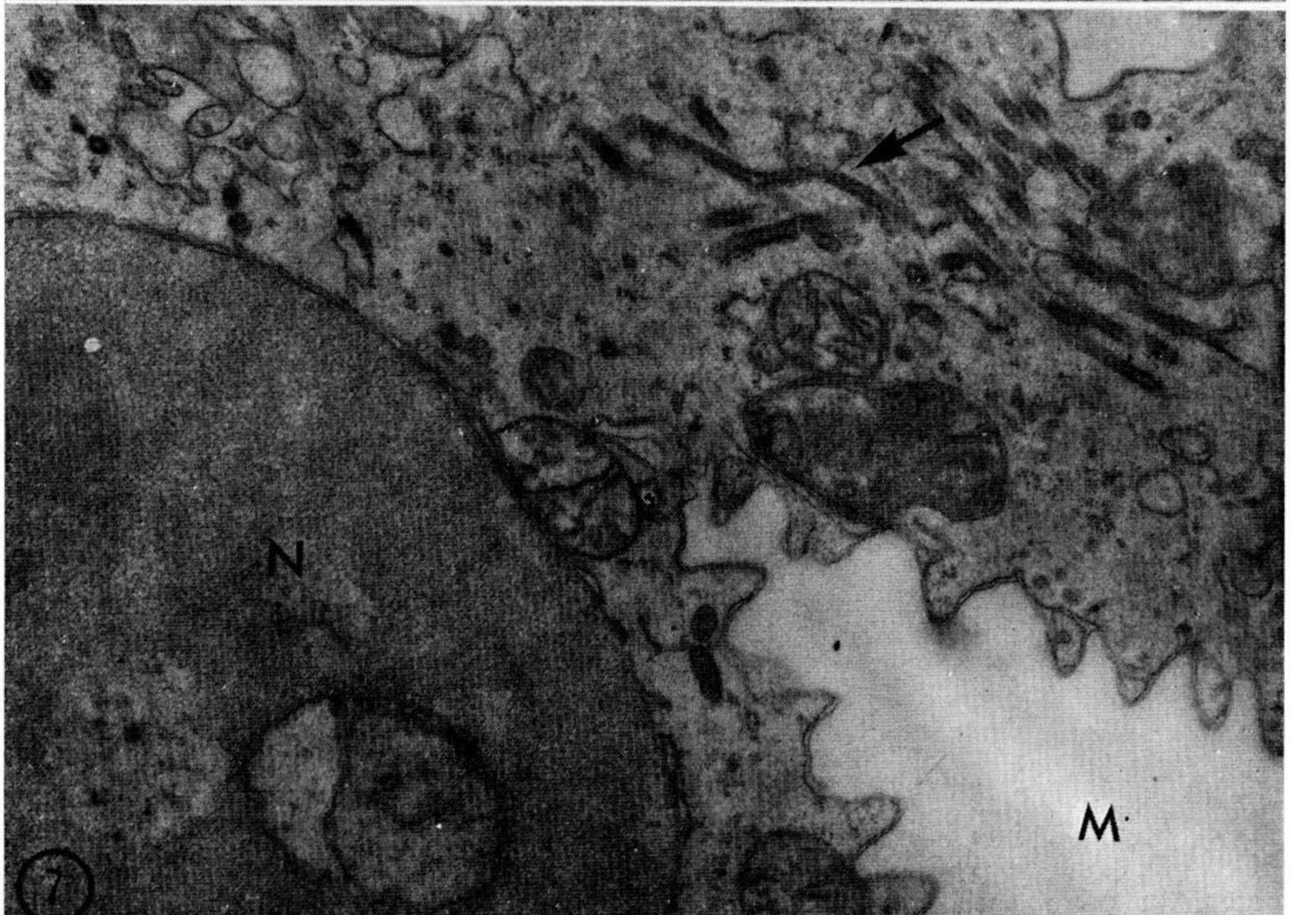
Fig. 6. — Methylcholanthrene spaces (M) with "saw-tooth" margins. A few particles (arrows) sectioned transversely are seen in the cytoplasmic matrix. x20,000.

Fig. 7. — The wall of the empty space left by the dissolved methylcholanthrene (M) has a double membrane. The majority of the particles are seen longitudinally, appear as cylindrical filaments, and show "bending" (arrow). Within the nucleus (N) of this reactive cell there is a possible inclusion body. x31,000.


M
M
6


N
M
7

implantation and in both animals examined three months later. They were cylindrical or filamentous in form and had central or axial holes or cavities. When cut longitudinally they appeared as long filaments with a clear axial space. On transverse section, however, they had the appearance of "doughnuts" with outer and inner shells. The inner shell was more electron-dense than the outer. All particles were uniform in size. Their fine structure was completely identical with that of the particles identified in the intracerebral lesions induced with dibenzanthracene and with those in the extracranial carcinogen-induced lesions. The diameter of the outer and inner shells measured approximately 77 mμ and 38 mμ respectively. The inner shell consisted of 10 to 13 fine granules arranged in a circle when viewed in transverse section and were 20 in number over a distance of 180 mμ in longitudinal section. Within the axial hole, when a particle was viewed transversely, there was a single electron-dense granule which approximated the size of a ribosome; longitudinal views of the cylindrical particles disclosed several ribosome-like granules dispersed within the inner space. At least one end of the axial holes communicated freely with the cellular cytoplasm (Fig. 8). The length of the particles seemed variable.

The co-existence of electron-dense, lipid-like laminated bodies were noted frequently (Figs. 8 and 11). No direct relationship, however, was noted between the particles and these dense bodies.

It should be noted that there were certain morphologic variations in a few particles (Figs. 11, 12, 13 and 14). Some of them lay within the endoplasmic reticulum (Fig. 13, thick arrows). In such instances, the outer shells were continuous with the membrane of the endoplasmic reticulum. Another morphologic variation was the continuity of the outer shells of adjacent particles (Fig. 14, thin arrow). A further variation was a so-called tail-like structure of a few particles (Fig. 14, thick arrow), although this could conceivably have resulted from the direction of sectioning of the particles within the endoplasmic reticulum. Finally, "bending" of the cylindrical particles was also noted in rare instances; at these sites possible "segmentation" could occur (Fig. 7, arrow).

Benzpyrene

The pellets of benzpyrene were implanted at various sites in the right cerebral hemispheres, producing reactions in the cerebral cortex, the subcortical white matter, Ammon's horn formation and the vicinity of the lateral ventricle. With the light microscope, portions of the pellets were noted among the reactive cells or within their cytoplasm. They appeared as needle-shaped empty slits which resulted from

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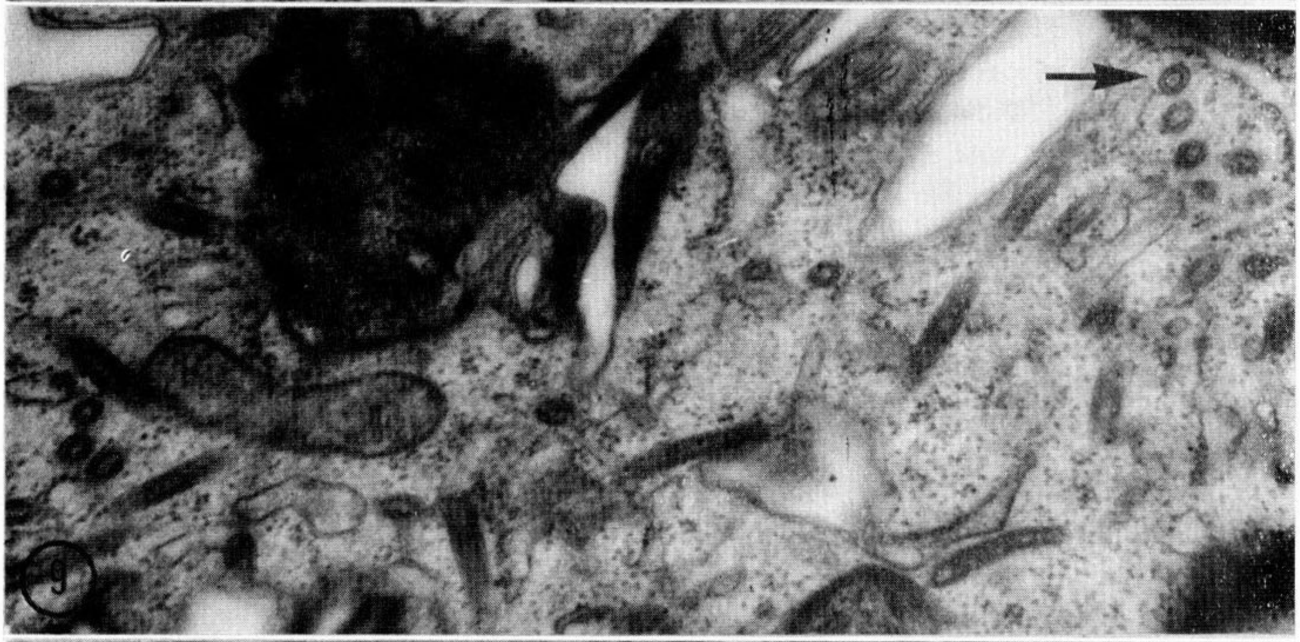
Fig. 8. — Longitudinal view of rods to show axial holes within which may be seen small, round, electron-dense cores resembling ribosomes and measuring 100 to 150A. The length of the particles seems variable; at least one end opens freely into the cytoplasm. Note laminated electron-dense body (LD). x40,000.

Fig. 9. — Particles seen transversely as well as longitudinally. Note "doughnut" appearance produced by inner and outer shells, as well as dense axial core in central hole (arrow). x40,000.

Fig. 10. — Transverse view of many filamentous rods, disclosing the "doughnut" configuration. The smaller, round, electron-dense granules are ribosomes. x55,000.


LD
8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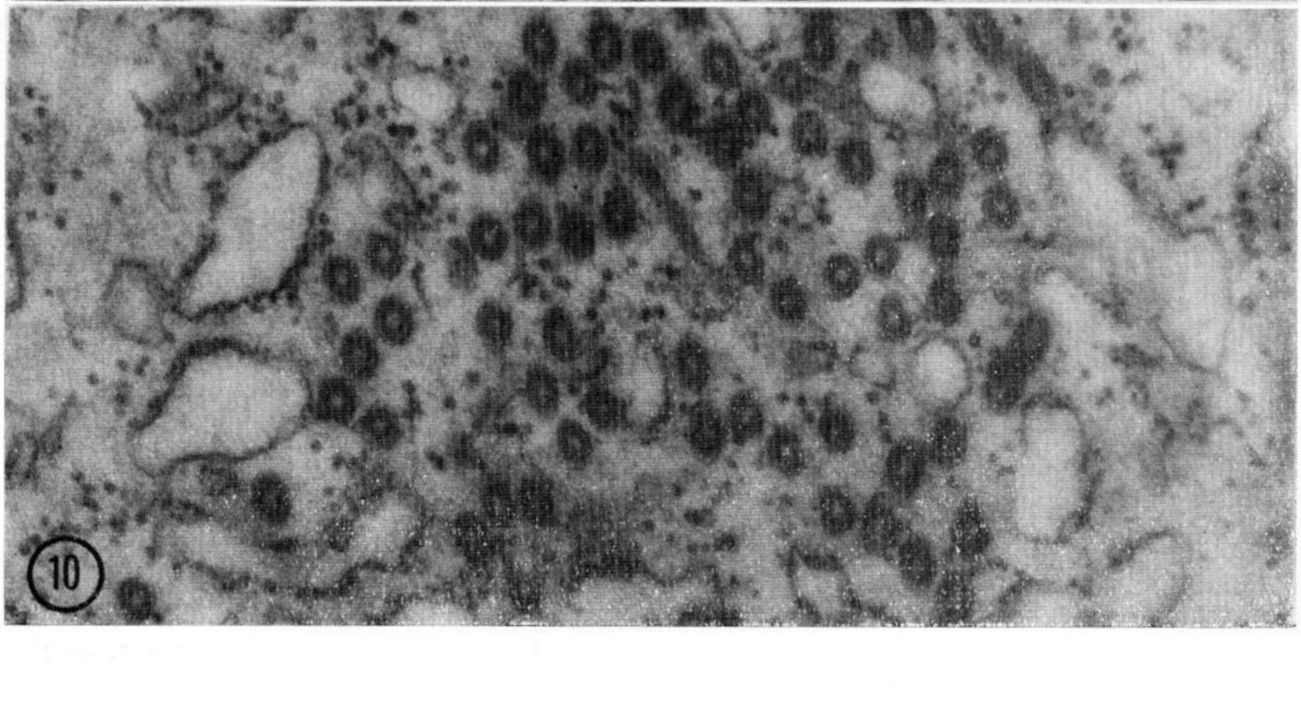
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the solution of the hydrocarbon by the ethanol and acetone. These slits or cavities on occasion were oblong in shape and all had smooth walls (Fig. 16).

Under the electron microscope, benzpyrene crystal spaces were mainly needle-shaped and lay both between the reactive cells and within their cytoplasm in a manner quite similar to that produced by methylcholanthrene and dibenzanthracene. Cylindrical filamentous particles were present in eight of the 11 mice examined: both animals examined at two months after implantation had particles; three animals of the five examined at three months had them; three of the four examined at nine months were positive. The localization of the particles as well as their fine structure within the reactive cells in the lesions produced with benzpyrene were the same as with dibenzanthracene and methylcholanthrene. The particles were always found near the empty spaces produced by the chemical; they were multitudinous and lacked a characteristic arrangement pattern. They often accompanied electron-dense, laminated bodies of lipid composition (Fig. 15). In most instances they were located in the cytoplasmic matrix, but in a few exceptional cases they were found within the endoplasmic reticulum, as was noted in lesions produced with other carcinogens.

The fine morphologic details of these structures are illustrated in both longitudinal and cross section views in figures 17 and 18. Longitudinal views revealed that the rods had axial holes which were seen as clear axial bands. The length of these cylindrical rods was variable. Rather large, dense granules were found within the axial bands; these dense granules were approximately the same size as the ribosomes (100 to 150A). They were osmophilic and stained well with uranyl acetate. On cross section, the cylindrical particles appeared as "doughnuts" with dense inner and less dense outer shells. The inner shell consisted of fine granules arranged radially and measured about 38 mμ in diameter. The outer shell measured approximately 77 mμ in diameter.

COMMENT

In previous studies with dibenzanthracene, particles of cylindrical or filamentous form were found in almost all lesions during the precancerous stage[11]. In the present investigation with methylcholanthrene and benzpyrene, completely similar cylindrical particles were noted. Three of the four animals treated with methylcholanthrene were positive, and eight of the 11 animals implanted with benzpyrene were found to have the filamentous rods. But it should be emphasized that the failure to find these rods does not necessarily indicate their total absence in these animals. This is because the random samples of the lesion examined with the electron microscope probably represent less than one hundredth of its whole size.

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Fig. 11. — The dissolved out carcinogen has left clear spaces (M) lined by "saw-tooth" margins. The cylindrical particles or rods (arrows) are near these spaces. Laminated electron-dense bodies (LD) are also noted. The nucleus (N) of one reactive cell is seen in lower left corner. x23,000.

Fig. 12. — Light micrograph of carcinogen space. Vestopal embedding; Bielschowsky's silver impregnation; x600.


M
LD
N
M
11
12

There is yet another consideration to which attention should be called. From previous experiments with intracerebral tumors induced with carcinogens it was shown that the first glioma following implantation of methylcholanthrene occurred on the 127th day[22]. Also, after benzpyrene implantation the first tumor to appear was on the 174th day[23]. The average appearance time of tumors induced with both carcinogens was considerably longer. From this it can be seen that the filamentous rods which were found in the animals of the present study occurred in lesions well within the precancerous period. Indeed, histologic examination of each lesion failed to disclose tumor cells. Earlier experiments revealed the fact that when neoplasia does actually arise as verified by microscopic examination, the cylindrical rods are no longer found.

The precise nature of these rods is still unknown. There are certain morphologic similarities between them and the cilia of ependymal cells. But the measurements of these two structures are entirely different. Moreover, rods were seen in lesions far removed from ependyma and were even found, as noted earlier, in extracranial lesions[12]. Another intracytoplasmic organelle with a somewhat similar structure is the centriole[6]. Again, however, the filamentous particles have completely different measurements. In addition, the particles are found in vast numbers within the cytoplasm. The spindle fibers of cells in mitotic division must also be considered. Our filamentous rods, however, could not be correlated with mitotic activity. Porter found the length of the filaments in mitotic cells of rat sarcoma 4337 to be between 0.5 μ and 10 μ and their width to measure about 100 mμ; but strands as thin as 50 mμ and as thick as 200 mμ were also seen[16]. The spindle fibers of normal cells in mitotic division and of Rous sarcoma cells were found by DeHarven and Bernhard to measure 20 mμ in diameter[6]. The outer membrane of the lamellas in the spindle fibers of mitotic cells of the Walker 256 carcinoma were reported by Buck to measure between 60 and 350 A. All these measurements are at great variance with the rods here reported. Could these rods represent non-specific cytoplasmic organelles in cells which reacted to foreign bodies? Earlier observations seemed to exclude this possibility[11]. None of the reactive cells in tissue injected with cholesterol, cotton fibers and beef fibrin contained these rods during the three months of observations.

Thus far it has not been possible to identify intracytoplasmic organelles which correspond closely with the morphologic details of the cylindrical rods produced in brains of animals into which carcinogenic chemical compounds were implanted. There is striking similarity, on the other hand, between the fine structure of these rods and that of viruses, particularly the tumor viruses. Bernhard[2] reported the existence of a filamentous form of the polyoma virus, but considered it an exception to the usual form. He stated that, "It is not yet known whether this form is the

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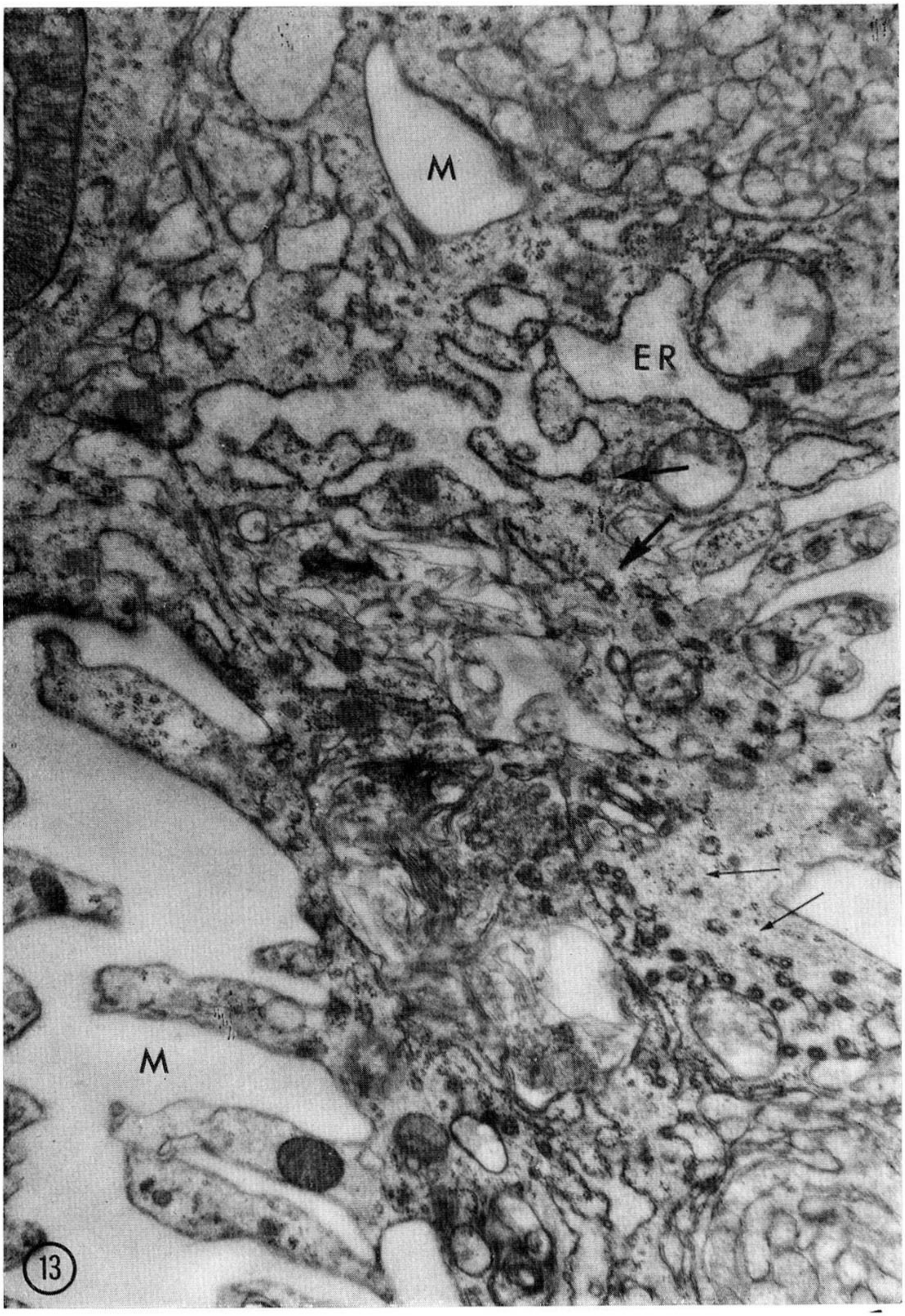
Fig. 13. — Higher magnification of a portion of figure 11, showing several particles (arrows). Some lie in the cytoplasmic matrix (thin arrows), but a few (thick arrows) are seen in the endoplasmic reticulum (ER) which is distended and contains pale granular material. In such instances the outer shells of the particles are continuous with the membranes of the endoplasmic reticulum. x33,000.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ER
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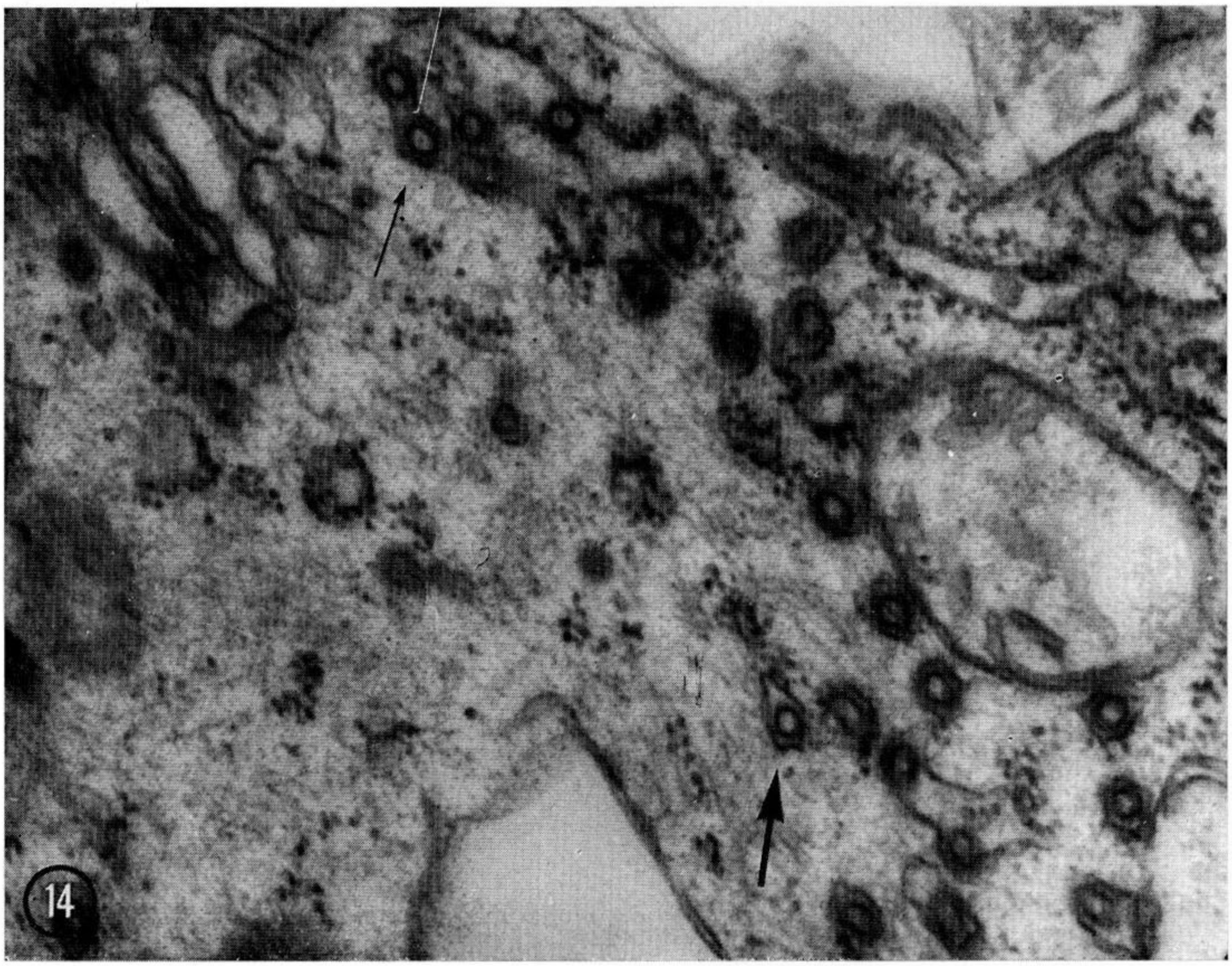

Fig. 14. — Particles within the endoplasmic reticulum. Note continuity of outer shells of two adjacent particles (thin arrow) and "tail-like" structure of one (thick arrow). x80,000.

necessary precursor of the mature virus or whether it appears only under some favorable conditions of growth". Howatson and Almeida[10] also noted filaments with a diameter of 38 mμ along with the spherical type of polyoma virus, and suggested that the filaments may represent a stage in the development of the common spherical particles. In a communication on the Moloney leukemia virus, Dalton[5] noted the presence of a "cylindrical form" among the typical spherical particles whose diameter is 100 mμ. Attention was called to the continuity which sometimes exists between the outer shells of two adjacent particles (Fig. 14) in our experiments. This continuity was also noted by Dalton in the Moloney leukemia virus.

Certain fine morphologic details of our rods are also seen in the tobacco mosaic

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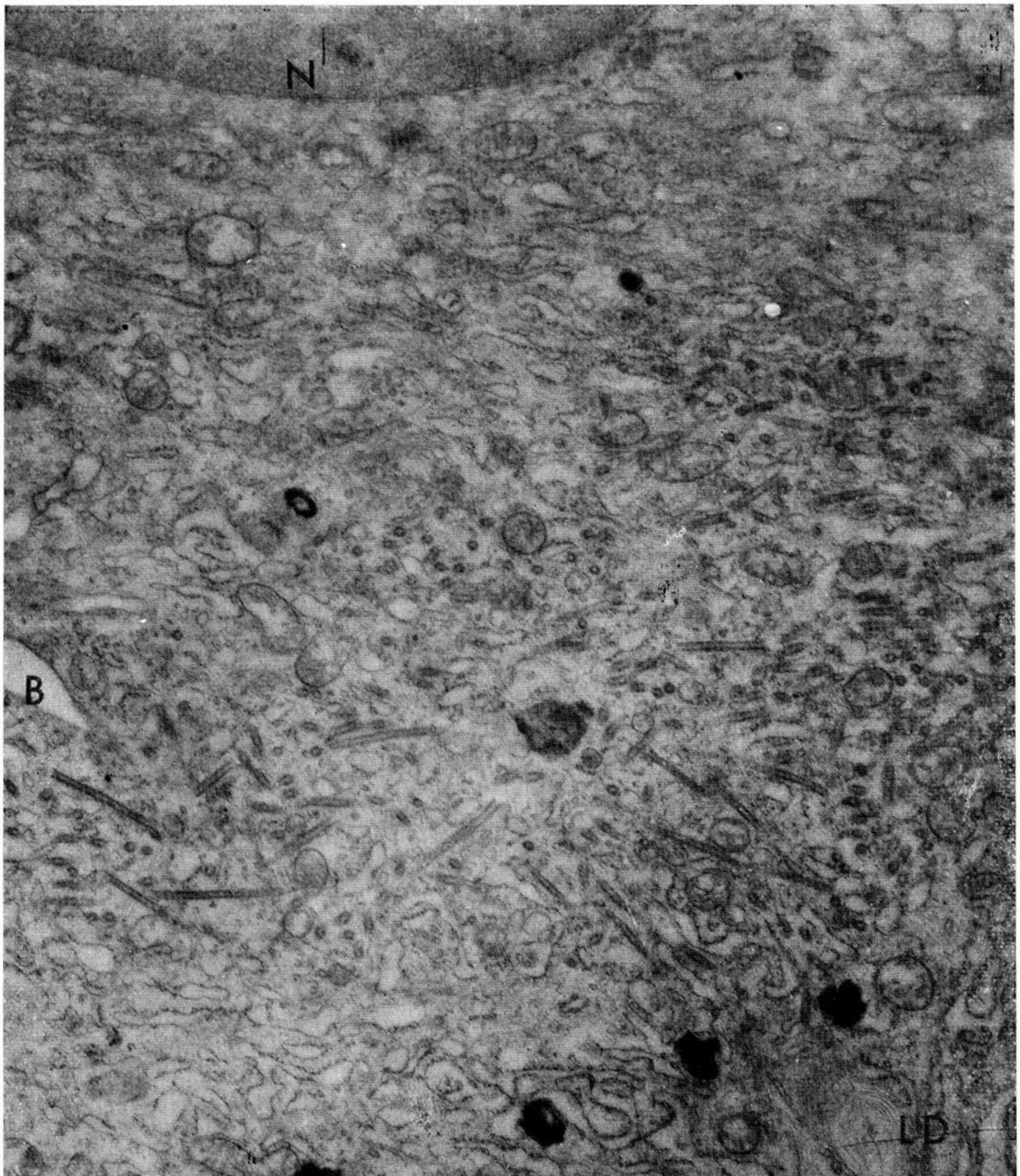
Fig. 15. — Numerous cylindrical or filamentous particles in cytoplasmic matrix, especially near the empty benzpyrene space (B). A laminated dense body (LD) is to be seen as well as the nucleus (N) of a reactive cell. x20,000.

Fig. 16. — Light micrograph from same block which yielded figure 15. Needle-shaped empty benzpyrene spaces (B). Vestopal embedding; Bielschowsky's silver impregnation; x400.


N
B
LD
15
B
16

virus, the well known rod-shaped plant virus whose mean diameter is 150 A and whose length is 2980 A [8, 10]. This particle also has an axial hole which measures 20 A in diameter and has 16-1/3 protein subunits around it. In spite of differences in size, the fine structure of these two particles is quite similar.

"Bending" and "segmentation" of particles illustrated in figure 7 (arrow) have also been noted in the polyoma[10] and Rabies virus[13].

An effort was made in this study to search for the origin of the cylindrical filamentous rods. They occur repeatedly in tissues which have been implanted with the carcinogenic polycyclic hydrocarbons 1, 2, 5, 6-dibenzanthracene, 20-methylcholanthrene and 3,4-benzpyrene. There is no difference among these chemical compounds as regards their association with the intracytoplasmic particles. This is in striking contrast to the failure to find particles in tissues which have been implanted with a variety of foreign bodies. The rods have been found exclusively near the carcinogenic chemical compounds. These osmophilic rods have a close association with the endoplasmic reticulum and with the ribosomes. These findings seem to indicate that the rods are the products which result from the interaction of the chemical carcinogens and certain cell components, in a manner perhaps similar to that achieved by Fraenkel-Conrat and Williams[7] who demonstrated the reconstitution of active tobacco mosaic virus from its inactive protein and nucleic acid components.

SUMMARY

The carcinogenic polycyclic hydrocarbons methylcholanthrene and benzpyrene, when implanted into the brains of C3H mice, induced lesions which were studied with the electron microscope. During the precancerous stages of the lesions there developed intracytoplasmic cylindrical filamentous rods which were characterized as follows: The length was variable but many times the transverse diameter; they were osmophilic; each had an outer and an inner shell; there was a hollow axial hole within the inner shell in which were dispersed electron-dense axial cores which resembled ribosomes; the inner shell was formed by fine electron-dense granules; on cross section the rods had the appearance of "doughnuts" with the outer shells measuring 77 mμ in diameter and the inner shells 38 mμ. These rods were usually present in the cytoplasmic matrix of the reactive cells, but occasionally they were found in the endoplasmic reticulum. They were always close to the carcinogenic chemical. Their morphology closely resembles several oncogenic viruses.

The possibility was discussed that these rods were the products of the interaction of the chemical carcinogen and certain living cell components.

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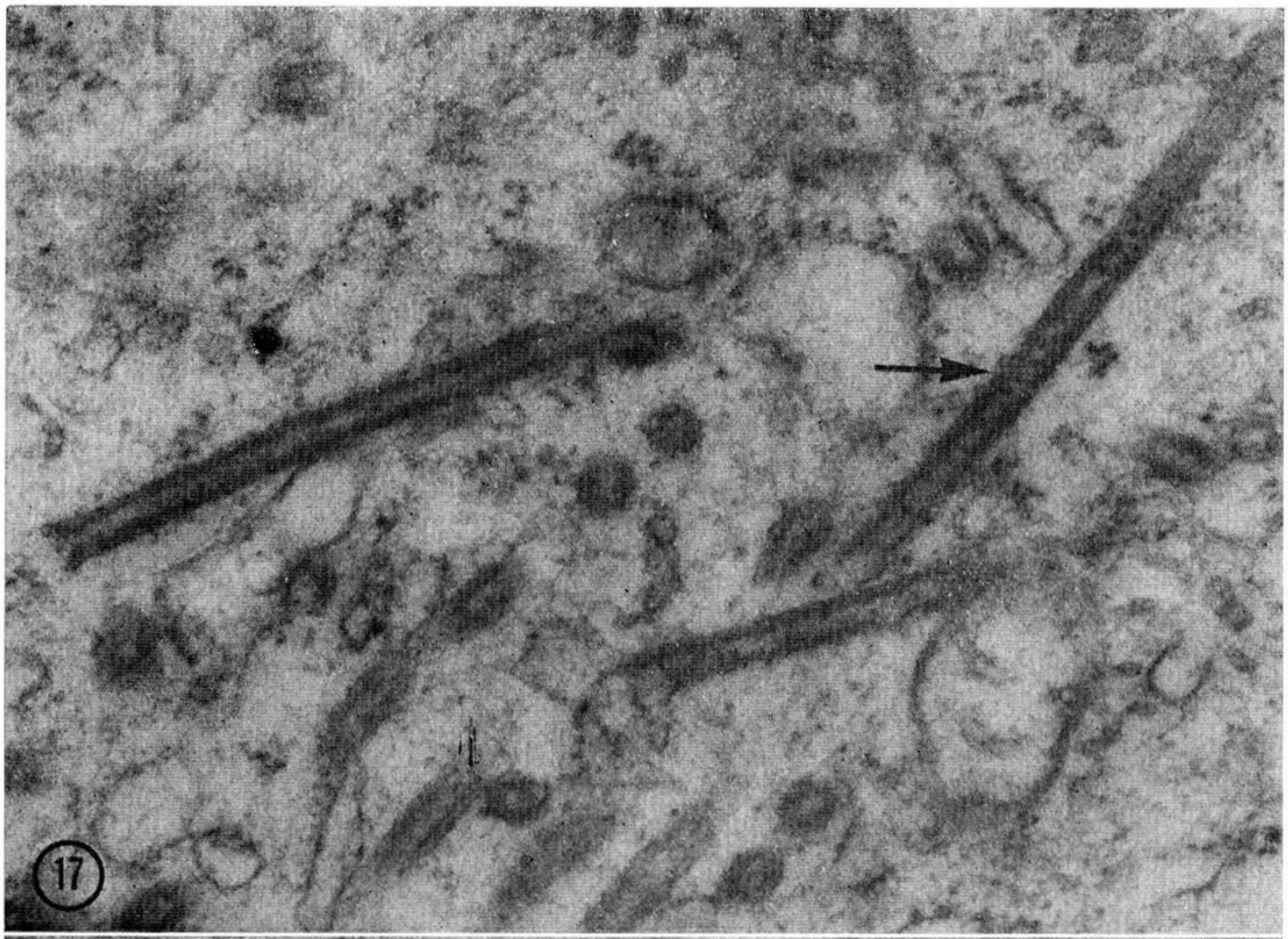
Fig. 17. — Fine structure of cylindrical particles in lesions induced by benzpyrene. Note identity of these particles with those in lesions due to methylcholanthrene. Several electron-dense axial cores are shown (arrow). x78,000.

Fig. 18. — Same section illustrated in figure 17, showing particles in transverse view. x78,000.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RESUMEN

La implantación de los hidrocarburos policíclicos carcinógenos metilcolantreno y benzpireno en cerebros de ratas C3H dio lugar a lesiones que fueron estudiadas con el microscopio electrónico. Durante las etapas precancerosas de las lesiones se formaron bastones filamentosos cilíndricos intracitoplasmáticos que presentaban las siguientes características: largo variable aunque varias veces mayor que el diámetro transverso; osmófilos; cada uno de ellos presentaba una vaina exterior y otra interior; dentro de ella su eje era hueco en el que se hallaban dispersados núcleos axiales densos que se asemejaban a los ribosomas; la vaina interna estaba formada por finos gránulos densos; al corte transverso tenían la apariencia de una pequeña rosca siendo el diámetro de la cubierta exterior de 77 mµ y el de la interior de 38 mµ.

Generalmente se hallaban en la matriz citoplasmática de las células reactivas, pero a veces fueron encontrados en el retículo endoplasmático. Siempre se encontraron en las proximidades de la sustancia química carcinógena. Desde el punto de vista morfológico son muy similares a algunos virus oncógenos.

En este trabajo se discute la posibilidad de que estos bastones hayan resultado como consecuencia de la interacción de sustancias químicas carcinógenas con ciertos elementos de la célula viva.

RÉSUMÉ

L'implantation des hydrocarbures polycycliques carcinogènes methylcholanthrène et benzpyrène dans des cerveaux de rats C3H a fait apparaitre des lésions qui ont été étudiées à l'aide du microscope électronique. Pendant les étapes précancereuses des lésions il se formèrent des bâtons filamenteux, cylindriques, intracytoplasmatiques qui présentaient les caractéristiques suivantes: longueur variable bien que plusieurs fois plus grande que le diamètre transverse; osmophiles; chacun d'eux présentait une gaîne extérieure et une gaîne intérieure; dans celle-ci on a pu observer une ouverture axielle, dans laquelle étaient dispersés des noyaux axiels pareils à des ribosomes electron-dense; la gaine intérieure était formée par de petits grains très fins et electron-dense; soumises a une section transverselle ils ressemblent à des "doughnuts", le diamètre de la gaine extérieure étant de 77 mµ et celui de l'intérieure de 38 mµ.

En général on pouvait constater leur présence dans la matrice cytoplasmatique des cellules réactives, mais parfois il furent trouvées dans le reticulum endoplasmatique. On les a toujours vus près de la substance chimique carcinogène. Du point de vue morphologique ils ressemblent à quelques virus oncogènes.

Dans ce travail on discute la possibilité que ces bâtons soient le résultat de l'interaction de substances chimiques carcinogènes avec certains éléments de la cellule vivante.

ZUSAMMENFASSUNG

Die karzinogenen polyzyklischen Kohlenwasserstoffe Methylcholanthrene und Benzypyrene verursachen nach ihrer Einpflanzung in die Gehirne von C3H-Maeusen Laesionen, die mittels Elektronien-mikroskop studiert wurden. In den praekarzinomatoesen Stadien der Laesionen beobachtet man die Entwicklung von intracytoplasmatischen zylindrischen filamentoesen Staebchen von folgenden Eigentuemlichkeiten; die Laenge war verschieden und mehrere so gross wie der Durchmesser; sie waren osmophil; sie hatten eine aeussere und eine innere Schale, in welcher axiale Koerner verstreut waren, die Elektron-undurchgaengig waren und die Ribosomen aehnlich sahen; im Querschnitt sahen die Staebchen wie "dough-nuts" aus, bei denen der Durchmesser der aeusseren Shale 77 millimicron und der inneren Schale 38 millimicron betrugen.

Die Staebchen befanden sich gewoehnlich in der cytoplasmatischen Matrix der reagierenden Zellen, jedoch wurden sie gelegentlich auch im endoplasmatischen Retikulum gefunden. Sie befanden sich immer in der Naehe der karzinogenen Substanzen. Ihre Morphologie war der verschiedener oncogenen Virus aehnlich.

Es wurde die Moeglichkeit eroertert, dass die Staebchen Produkt der Interaktion zwischen den chemischen karzinogenen Substanzen und gewisser lebender Zelbestandteile sind.

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Localization of Brain Tumors by Angiography

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Angiography is now widely used for the localization of supratentorial tumors and it is also valuable for some posterior fossa masses. It has the advantage that in many cases it may not only demonstrate the position of the tumor but it also may indicate the histology.

Technical Considerations

When a supratentorial mass is suspected it is usual to inject the common carotid artery, but occasionally, when a meningioma is suspected, it is helpful to thread the needle into the external or internal carotid arteries to achieve selective opacification of these vessels. Because local and general changes in the speed of the circulation are of considerable diagnostic importance, a standard quantity of contrast should be injected at a known rate, preferably by means of an automatic injector. A satisfactory technique is to inject 10 cc of 60 % Renografin in 1 second (8 cc is sufficient for an internal carotid injection or 6 cc for the external carotid or vertebral arteries).

Films are taken at 2 films a second for 3 seconds and then 1 film a second for the subsequent 4 seconds, a total of 10 films. It is an advantage to use a simultaneous biplane technique so that the anterior-posterior and lateral projections are obtained with one injection and also the corresponding anterior-posterior and lateral films taken at the same time will have exactly the same vessels filled, which makes analysis of the films somewhat easier.

Some of the angiographic changes caused by tumors will now be described.

Stretching of Vessels

The vessels adjacent to the tumor tend to lose their normal undulations and become straightened or curved with the concavity of the curve directed toward the center of the tumor. This change generally indicates an increase in the size of the gyri on each side of the vessel because the gyri are involved by tumor, or, even more commonly, because they are involved by edema surrounding the tumor. A vessel which lies at the margin of the tumor may show quite marked curvature because it receives all of the pressure of the tumor from one side while a vessel which crosses the tumor somewhere between its margin and central axis shows less marked curvature because it is being compressed by unequal forces acting from either side [3]. The stretched vessels may also be reduced in diameter.

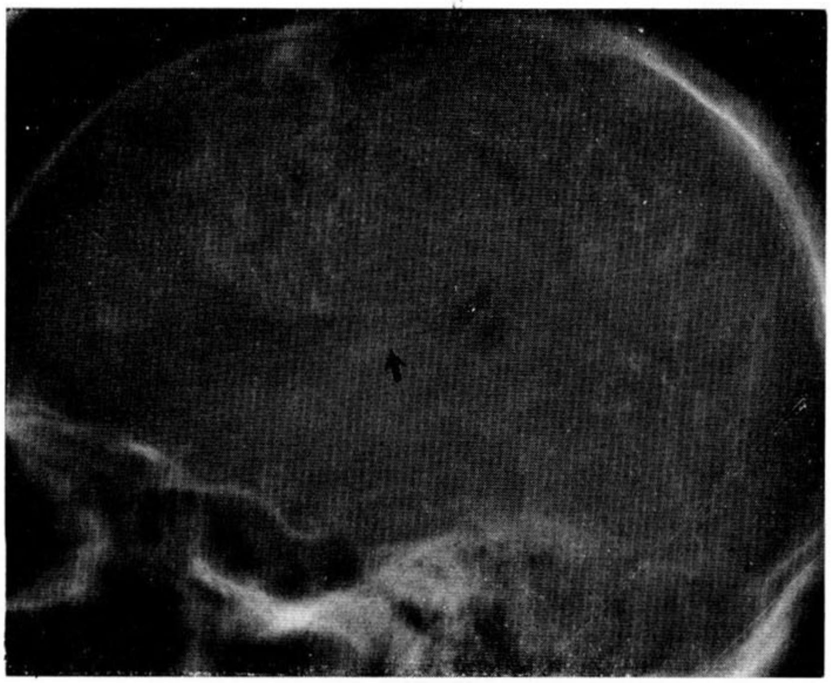


Fig. 1. — *Highly malignant glioblastoma showing coarse tumor vessels and early opacification of deep and superficial veins. — (a) Lateral view, late arterial phase, showing the tumor vessels draining into a surface vein (upper arrow) and the thalamostriate and internal cerebral veins (lower arrow). The thalamostriate vein and anterior part of the internal cerebral vein are depressed.*

Tumor Circulation

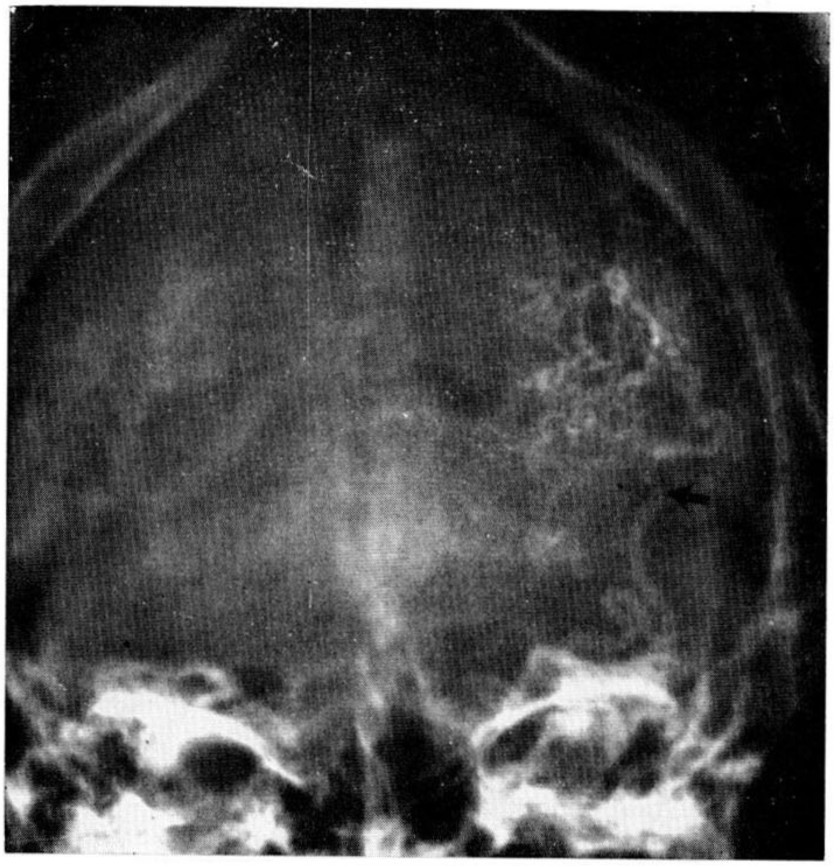
Because many glioblastomas, metastases, and meningiomas are much more vascular than normal brain, they may show a blush or stain in the angiogram. Surprisingly little has been written about the precise criteria which enable us to recognize a tumor stain in an angiogram, but it may be said that the normal arteries of the brain branch in a fairly regular manner, and as they branch they become progressively smaller. The course and distribution of the branches follows a systematic pattern. In an area of tumor vessels, there is not only an increased number of vessels, but the vessels may vary in caliber along their length and the branching pattern is completely erratic. Some of the features of tumor stains have been discussed by Wickbom [7].

The most malignant glioblastomas have very coarse tumor vessels and evidence of rapid shunting from arteries to veins so that veins may be opacified even in the arterial phase. (Fig. 1). Less malignant glioblastomas are associated with fewer and shorter tumor vessels, often of smaller diameter, and with evidence of slower shunting of blood from arteries to veins or no evidence of shunting. Occasionally me-

(b) Anterior-posterior view. The internal cerebral vein (arrow) is displaced across the midline.

tastases may show coarse, wide tumor vessels but there is usually a slower shunting of contrast from arteries to veins than in the most malignant glioblastomas. More commonly metastases show shorter and thinner tumor vessels or they may be relatively avascular. Hemorrhage, necrosis or cyst formation will give a local avascularity. An abscess may show a central avascular area surrounded by crowded normal vessels and a circular coursing vein may be seen in the venous phase.

Meningiomas are usually quite rich in vessels which are smaller and show more regular architecture than glioblastomas. The great abundance of capillaries cau-



2 a

2 b

Fig. 2. — *Meningioma shown by external carotid arteriography. — (a) & (b) Anterior - posterior and lateral views showing a large external carotid branch (arrow) supplying an occipito-parietal meningioma.*

ses the tumor stain to have a homogeneous density which is generally seen in the late arterial or venous phases. (Fig. 2). Internal and external carotid injections may fill two separate areas of tumor circulation. Occasionally metastases may show a blush very like a meningioma (Fig. 3) but the blush seen in metastases tends to disappear more quickly than most meningioma stains.

Local Increase in Speed of Circulation

An early vein signifying an increased speed of circulation may be seen without evidence of tumor circulation [4]. This finding may be present in some cases of glioblastomas, astrocytomas, metastases and meningiomas.

Local Decrease in Speed of Circulation

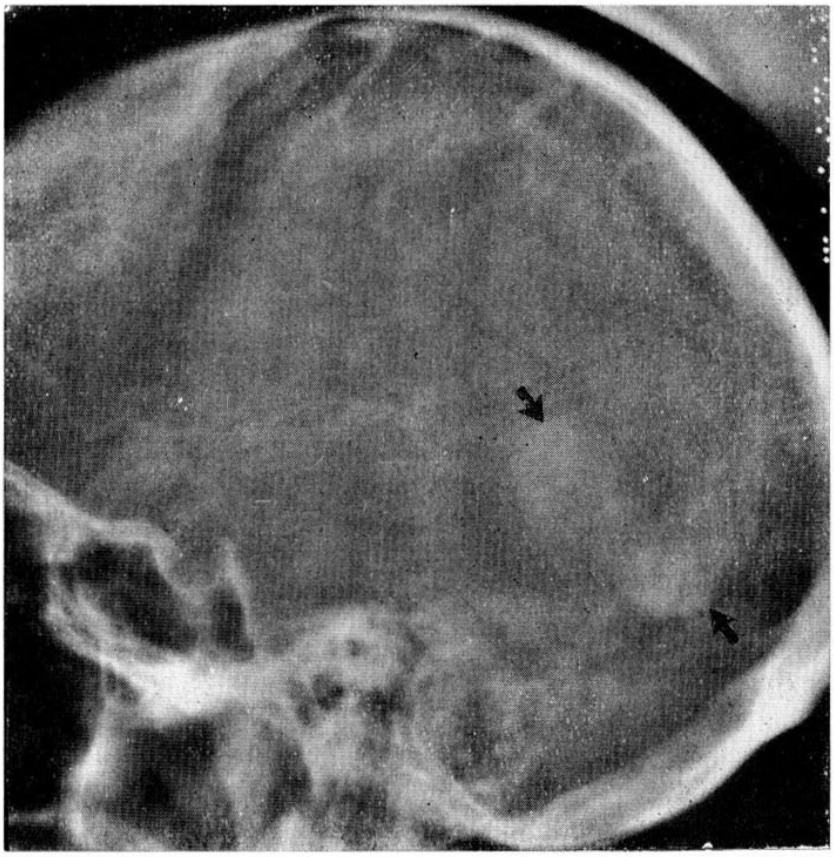
There may be delayed appearance of one or more arteries adjacent to the tumor. Slowing of the local arterial circulation may be seen in some metastases or gliomas and occasionally in meningiomas. Delayed appearance of local veins may be seen quite commonly when there is no evidence of a tumor blush in the angiogram, and less commonly, when tumor circulation is present (Fig. 4). These changes may be due to local pressure from the tumor or associated edema.

Avascular Area

An area of avascularity may be seen in an angiogram. Whenever a large avascular intraaxial tumor is demonstrated, the possibility of a cyst shoud be considered. Such an appearance may be caused by any avascular mass lesion including an abscess or hematoma.

Displacement of Vessels

In general, vessels are displaced away from a tumor, and those which are close



2 c

Fig. 2. — *Meningioma shown by external carotid arteriography. — (c) Lateral view, venous phase. There is a large area of homogenous tumor stain (arrows).*

to the tumor will be most markedly displaced. This basic pattern of the displacements may be modified if herniations are present. Before describing the displacements caused by different tumors some features of the normal pattern of the middle cerebral branches will be discussed briefly.

The middle cerebral trunk passes laterally between the temporal lobe and the lower aspect of the Island of Reil and it then turns backward and upward on the surface of the Island of Reil giving off a series of branches. Each of these branches passes rostrally on the surface of the Island of Reil as far as the junction of the insula and the fronto-parietal operculum where is turns caudally to emerge from the sylvian fissure and then each branch ascends on the surface of the brain (Fig. 5). If one joins the points where the middle cerebral branches ascending on the surface of the insula turn caudally, these points should lie on a straight line [6]. Occasionally one of the points will be a little above the line if the vessel passes deep into a sulcus at the top of its course or a little below if it strikes a gyrus at the top of its course. The different portions of these branches may usually be identified in anterior-posterior and lateral arterial phase films. The point where the most posterior middle cerebral branch lying on the insula turns down at the top of the insula is called the angiographic sylvian point. In anterior-posterior films the sylvian point will be the highest and most medial point on the vessels on the surface of the insula. In a lateral arteriogram film, if we draw a line along the top of the insula where the middle cerebral branches turn downward, a line joining the angiographic sylvian point to the point where the middle cerebral artery enters the depths of the sylvian fissure, and a line along the anterior branch ascending on the surface of the insula, we will form the "sylvian triangle" which is of great importance in the recognition of many supratentorial tumors [6]. In the standard anterior posterior view with at least a 40 inch target film distance and the head not more thant 1 ½ inches from the film the angiographic sylvian point normally lies between 30 and 42 mm from the inner table of the skull. Another use-

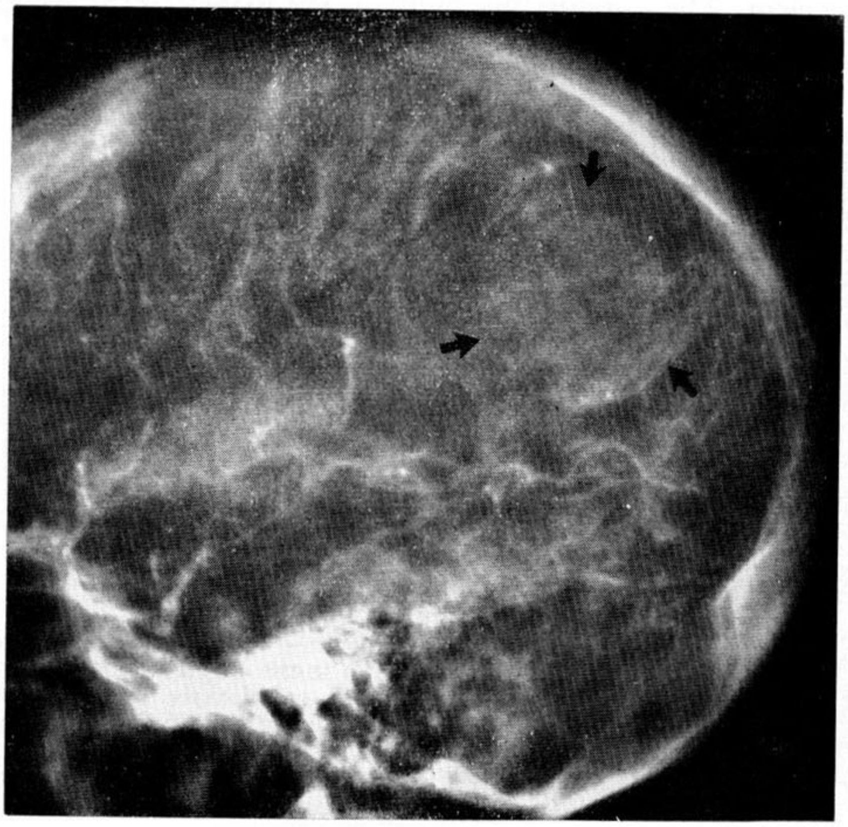


Fig. 3. — *Metastasis causing a stain (arrows) similar to the homogenous stain commonly seen in a meningioma.*

ful landmark in the lateral view of an angiogram is the clinoparietal line which joins the anterior clinoid process to a point 2 cm. above the lambda, or, if the lambda cannot be identified, 9 cm above the internal occipital protuberance. The lowest major branch of the middle cerebral artery should not be more than 1.0 cm above this line measuring at a point 2.0 cm behind the carotid siphon in adults (the first major branch may be as much as 1.5 cm above this line in children and 2.0 cm in infants).

In a frontal projection of a carotid angiogram the sylvian point is close to the center of the distance from the upper margin of the petrous pyramid (or the roof of the orbit, whichever is lower) to a horizontal line drawn tangential to the inner table of the skull. The normal sylvian point may be as much as 1.0 cm below the center of this distance (Fig. 6).

Displacement of the Anterior Cerebral Artery

In general, the portion of the anterior cerebral artery closest to a tumor will show the most marked displacement. The displacements of the anterior cerebral artery are, however, limited by the falx. This firm structure is relatively shallow anteriorly and deep posteriorly and the falx is rarely displaced from the midline even by very large mass lesions. Also the callosomarginal branches curve higher on the medial surface of the hemisphere than the pericallosal artery and they soon fall under the protection of the falx which prevents midline displacements. The pericallosal artery lies below the free margin of the falx until near the splenium of the corpus callosum and it may be displaced across the midline back to this point.

A low frontal tumor will displace the adjacent proximal portion of the anterior cerebral artery across the midline while a superiorly situated or more posteriorly placed tumor will displace the distal part of the pericallosal artery across the midline and there is a "step" where the pericallosal branches return to the midline where their midline shifts are limited by the falx (Fig. 7).

Frontal Tumors

The anterior cerebral artery is displaced across the midline, the displacement being most marked opposite the tumor. There

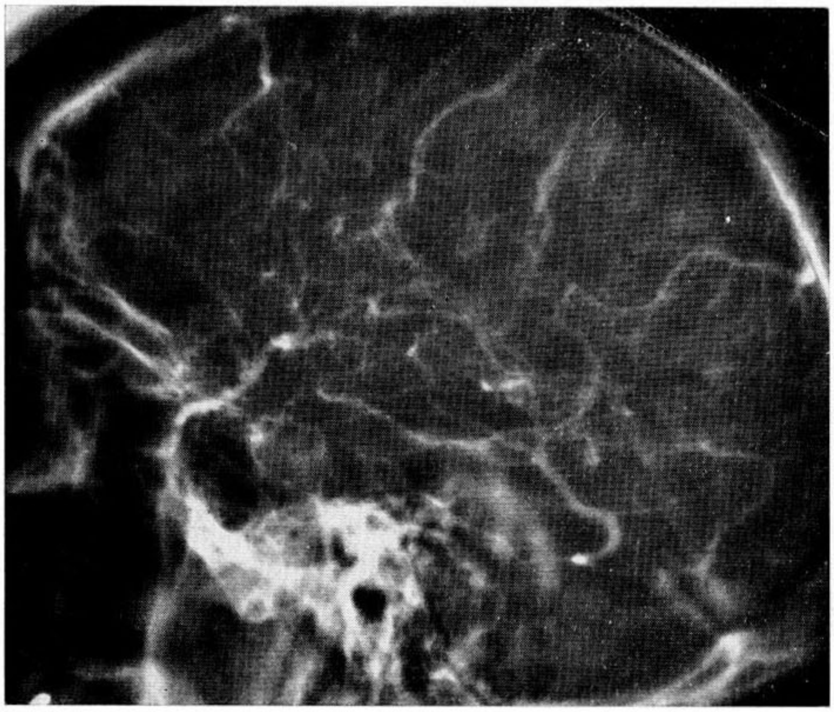
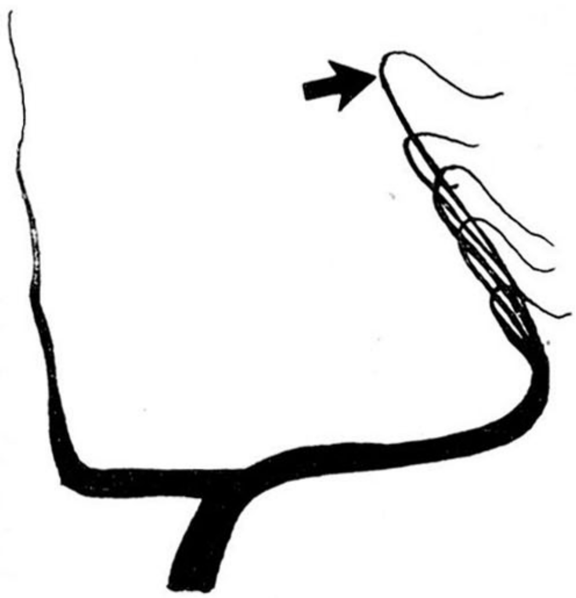


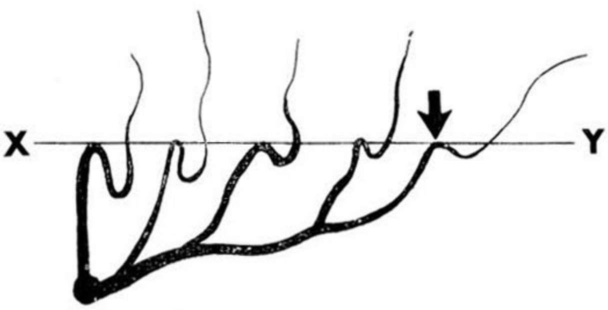
Fig. 4. — *Delayed appearance of a vein adjacent to a parietal metastasis. — (a) Lateral view 5 seconds after the injection of contrast showing most of the convexity veins clearly opacified.*

Fig. 4. — *Delayed appearance of a vein adjacent to a parietal metastasis. — (b) Lateral view at 7 seconds showing a vein (arrows) in the region of the tumor filling considerably later than the surrounding veins.*

may be posterior displacement of the anterior part of the sylvian triangle, or, if the mass is high in the frontal lobe, the anterior part of the sylvian triangle may be depressed. The carotid bifurcation may be displaced downward or backward depending on the relationship of the tumor to that vessel. The junction of the thalamostriate and internal cerebral veins will be displaced backward if the mass is in the anterior frontal region or downward if the mass is in the posterior frontal region and superiorly situated. The anterior end of the internal cerebral vein may be displaced across the midline, particularly when the tumor extends deeply. In these cases the tumor may be closer to the internal cerebral vein than the anterior cerebral artery and the vein will show more marked displacement than the artery. The septal vein is displaced upward if it lies above the equator of a frontal tumor and downward if it lies below the equator of the tumor.



(a)



(b)

Fig. 5. — *Diagram of branching pattern of the middle cerebral artery. — (a) Anterior-posterior view. Arrow indicates the sylvian point.*

(b) Lateral view. The line X — Y joins the middle cerebral branches where they reach the top of the Island of Reil. Arrow indicates the sylvian point.

It may also be displaced across the midline. A subfrontal mass such as a meningioma arising under the frontal lobe will elevate the anterior cerebral arteries which will lie in the midline if the mass is symmetrical, or away from the side of the larger mass if it is asymmetrical. When a mass arises in the inferior part of the frontal lobe, there will not be elevation of all of the branches of the anterior cerebral artery from the floor of the anterior form but some will be displaced downward and stretched by the tumor. Tumors arising in the anterior pole of the frontal lobe or extracerebral masses in this region will displace the anterior cerebral artery backward. When the mass is extra-axial, all of the branches of the anterior cerebral artery will be displaced backward, but when it is intraaxial some of the branches will not be posteriorly displaced but will be stretched around the tumor. A mass

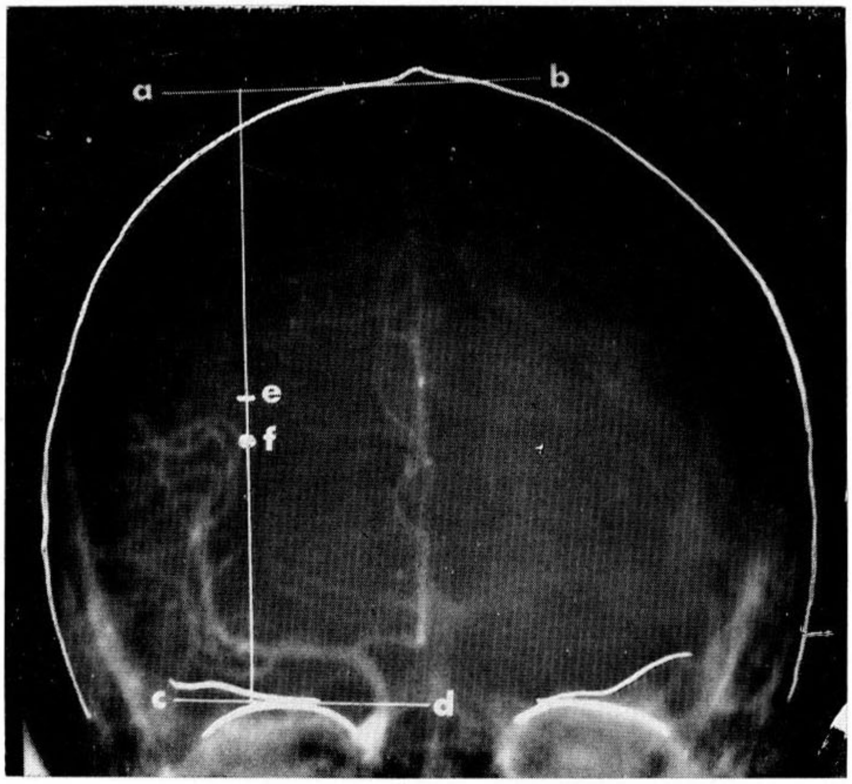


Fig. 6. — *Diagram to show the normal position of the sylvian point in the anterior-posterior view. Line a-b is a horizontal line through the inner table of the skull near the sagittal plane (excluding the groove for the superior sagittal sinus). Line c-d is a line through the superior orbital margin or the superior aspect of the petrous temporal bones, whichever is lower. A line is drawn through the sylvian point perpendicular to lines a-b, and c-d, and e is the mid point on this line. Point f should not be more than 1 cm. below point e.*

such as a falx meningioma arising medial to the frontal lobe will displace the pericallosal artery downward and will cause lateral displacement of the branches of the anterior cerebral artery on the medial surface of the frontal lobe.

Some frontal lobe tumors extend into the corpus callosum causing an increased sweep of the pericallosal artery and posterior displacement of the internal cerebral vein which shows increased separation from the pericallosal artery by the mass growing between the two vessels.

More posteriorly situated tumors in the upper part of the frontal lobe lie above the sylvian triangle wich is therefore depressed and its upper side is curved with the center of this curvature indicating the center of the mass [3]. The branches of the middle cerebral artery ascending over the surface of the brain are stretched and separated if the tumor is superficial. If the mass is medially situated the vessels on the surface of the insula may be laterally displaced, and if the mass is situated laterally these vessels may be displaced medially.

The distance from the sylvian point to the medial edge of the pericallosal artery was measured by Kricheff and Taveras [3] in a series of suprasylvian space occupying lesions and it was found that a measurement of greater than 50 mm. was good evidence of deep extension of the tumor.

Parietal Tumors

These lie above the posterior part of the sylvian triangle and therefore the sylvian point and the adjacent vessels on the surface of the insula are displaced downward. If the tumor lies in a plane lateral to the sylvian point it will displace the sylvian point medially, and if the tumor is medially situated it may displace the sylvian point laterally. The internal cerebral vein is frequently displaced across the midline and its curve is flattened. The anterior cerebral artery may be displaced across the midline and the

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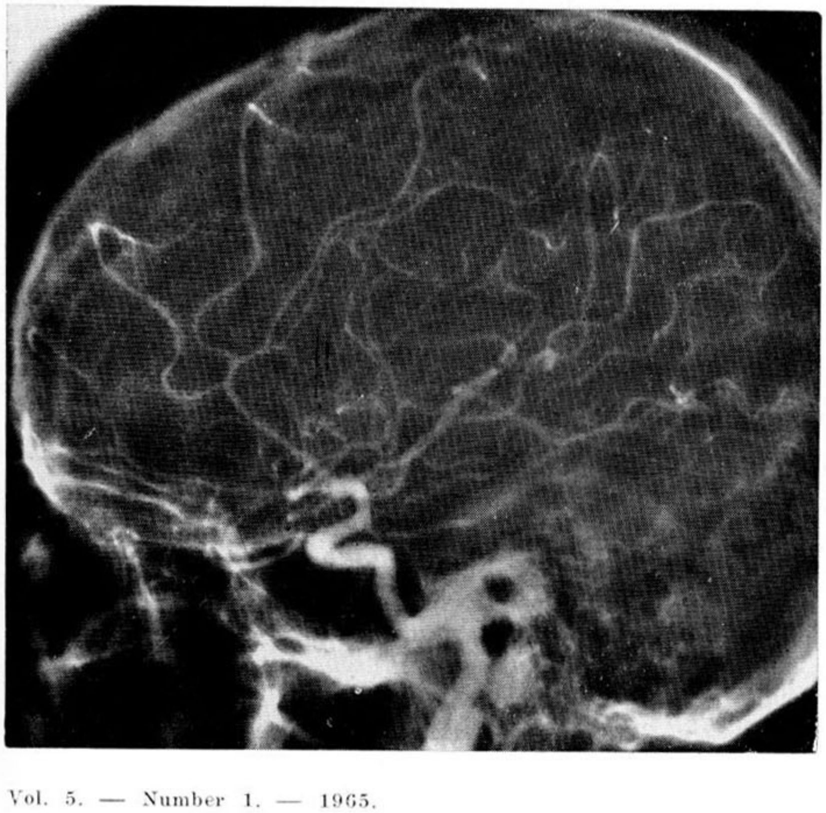


(2)

Fig. 7. — (a) Frontal glioma causing marked displacement of the anterior part of the anterior cerebral artery across the midline. There is stretching of most of the anterior cerebral branches in the frontal region and the anterior part of the sylvian triangle is depressed. — (1) Anterior-posterior view. (2) Lateral view.

displacement is most marked in the more distal part of the pericallosal branch which shows a step posteriorly where it returns to the midline. Displacement of the pericallosal artery across the midline is usually less marked when there is a posteriorly situated mass than with frontal masses of comparable size because the falx is deeper posteriorly and this reduces the midline displacements. A meningioma arising from the falx will displace the anterior cerebral branches laterally and may also depress the pericallosal artery.

Occipital Tumors

These cause straightening and separation of the medial occipital branches of the posterior cerebral artery and larger masses will displace the sylvian vessels forward [2]. The lateral choroidal vessels and the choroid plexus blush in the floor of the atrium may be seen to be displaced forward if a vertebral arteriogram is performed, or if there is good filling of the posterior cerebral artery from the carotid.

Temporal Tumors

Anterior temporal tumors tend to elevate the proximal part of the middle cerebral artery and the basal vein of Rosenthal is displaced medially and sometimes also elevated. The superficial temporal vein may also be elevated as it lies in the sylvian fissure [1].

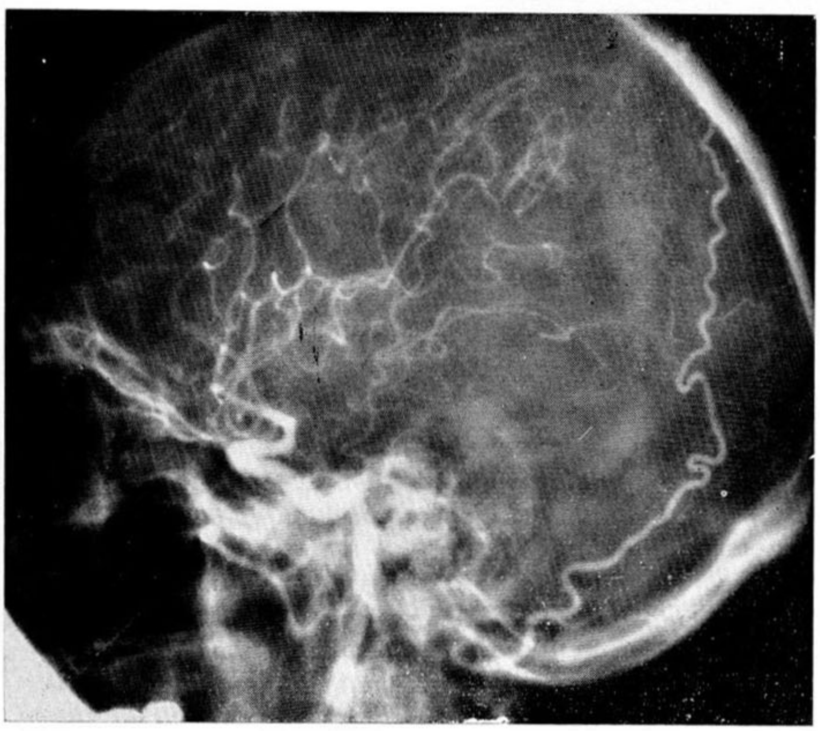
Posterior temporal tumors elevate the sylvian point and the distal portions of the middle cerebral artery. If the tumor is superficial to the plane of the sylvian point, it will displace the sylvian point medially, and if deep to the sylvian point, it will displace the sylvian point laterally. If these tumors extend posteriorly, the sylvian point will be displaced forward. The anterior choroidal artery may also be telescoped forward.

When an intraaxial temporal tumor extends deeply, in addition to lateral displacement of the vessels on the surface of the insula, the anterior choroidal artery tends to be displaced downward and laterally and the lenticulostriate arteries are displaced laterally if the bulk of the tumor is deep to these vessels. The posterior cerebral artery is displaced inferiorly and there is separation of the internal cerebral vein and the basal vein in the alteral view. When the tumor is intraaxial, the temporal branches of the middle cerebral artery will be "draped" over the tumor. Draping of the temporal branches of the middle cerebral artery is the appearance seen in these vessels when they extend upward (and usually also a little backward) from the main middle cerebral trunk and then downward and backward on the outer surface of the temporal lobe with elongation and straightening of the portions of the vessels on the surface of the temporal lobe. (Fig. 8). Most extracerebral tumors arising under the temporal lobe will elevate the temporal branches of the middle cerebral artery and medially placed extracerebral tumors elevate the anterior choroidal artery. Intracerebral masses may also elevate the anterior choroidal artery if the bulk of the tumor is below the choroid fisure. The posterior communicating and posterior cerebral arteries are elevated by medially placed extracerebral tumors and depressed by intracerebral tumors. Medially placed extracerebral tumors elevate the basal vein of Rosenthal usually without displacing it medially, and intracerebral tumors will displace this vein medially and may also elevate it when the greater part of the tumor is situated below the level of the temporal lobe tributaries of the basal vein.

Thalamic Tumors

These tumors lie close to the internal cerebral vein with most of the thalamus lying below the level of the vein and therefore the internal cerebral vein tends to be displaced across the midline and elevated at an early stage. In addition, the shape of the internal cerebral vein may be altered so that it no longer has its smooth curve but becomes irregular. The internal cerebral veins on the two sides are almost exactly superimposable in the lateral view in normal cases, but when a tumor develops in the thalamus the two veins may be separated. This separation may be detected by superimposing the lateral venous phase film of the right side on a similar film of the left side and a separation of the two internal cerebral veins is strong evidence of a mass in or near to the thalamus. The thalamostriate vein may be elevated particularly where it passes over the floor of the lateral ventricle. This is best seen in the anterior-posterior projection where the thalamostriate vein immediately ascends upward and laterally from the internal cerebral vein instead of having its normal downward curve around the floor

(1)



(2)

Fig. 7 — (b) Large occipito-parietal meningioma causing a distal shift of the pericallosal artery. The vessels forming the sylvian triangle are displaced forward and there is an avascular area in the occipito-parietal region. — (1) Anterior-posterior view. (2) Lateral view.

of the lateral ventricle. The basal vein may be displaced downward, backward, or laterally and the internal cerebral vein may be separated from the basal vein as seen in the lateral view. There may be elevation of the middle cerebral artery due to the rotation of the lower portion of the insula laterally. It is most important to recognize that moderate elevation of the middle cerebral artery may be caused by a thalamic mass, because, if this is not understood, it may be mistaken for a temporal tumor [5]. The anterior choroidal artery is usally displaced laterally and its more distal portion may pass round the posterior aspect of the enlarged thalamus. In the frontal projection there may be widening of space between the anterior cerebral and middle cerebral arteries, best shown by compressing the normal side while injecting the side of the tumor, which enables one to compare the vessels on the two sides. The lenticulostriate arteries may be displaced downward and laterally. Lateral displaced of the posterior cerebral artery or basal vein usually indicates brain stem extension of the tumor.

Other deep tumors may cause specific changes in an angiogram. For example, a colloid cyst of the third ventricle will cause elevation and lateral displacement of the anterior end of the internal cerebral vein while a tumor arising in the region of the pineal or quadrigeminal plate will elevate the posterior third of the internal cerebral vein. These tumors may also cause enlargement of the lateral ventricles which may be detected angiographically by the wide sweep of the thalamostriate vein in the anterior posterior view as it passes around the wall of the enlarged lateral ventricle. When the lateral ventricles are quite large, the pericallosal artery will show a wide sweep in the lateral view.

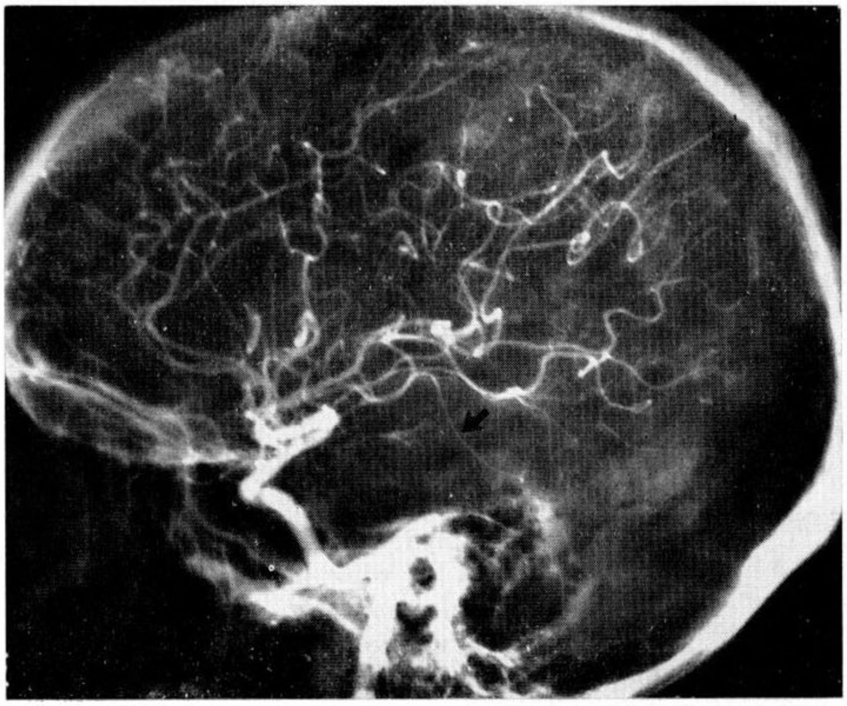


Fig. 8. — *Draping of the temporal branches (arrow) of the middle cerebral artery caused by an intra-axial temporal tumor. The middle cerebral trunk is slightly elevated.*

Posterior Fossa Tumors

These tumors are considerably more difficult to diagnose angiographically for various reasons: The posterior fossa is smaller than the supratentorial region and displacements caused by posterior fossa masses tend to be less marked. Also there are no major posterior fossa vessels which are normally in the midline as in the supratentorial region. The basilar artery may lie a considerable distance from the midline even in a normal subject. In addition, upward herniation through the tentorial opening and downward herniation through the foramen magnum tend to reduce displacements from the midline, even when a large laterally situated mass is present.

The displacements caused by posterior fossa masses will not be discussed in detail but it should be pointed out that it is a considerable advantage to perform arteriography for posterior fossa masses because some of the commoner posterior fossa tumors such as cerebellar hemangioblastomas and metastases may show a tumor blush, the most direct evidence of the position of a tumor.

SUMMARY

The angiographic changes caused by tumors include stretching of vessels, tumor circulation, local increase in the speed of circulation, local decrease in the speed of circulation, an avascular area and displacement of vessels. If all of these signs are to be appreciated, it is important to standardize the speed and quantity of contrast material injected. 10 cc. of contrast in 1 second is satisfactory for an internal carotid artery injection. The series of films must cover the entire arterial and venous phases. The sylvian triangle formed by the branches of the middle cerebral artery is defined and its importance in the localization of supratentorial masses is discussed. In general, vessels are displaced away from a mass lesion, and the vessels closest to the mass will show the most marked displacement. This basic pattern is altered when there are herniations of the brain because certain displacements are limited or modified by the falx and tentorium. The changes caused by frontal parietal, occipital, temporal and thalamic tumors are described. When the displacements of the vessels are relatively small it may be helpful to compare the vessels on the abnormal side with the normal side. The vessels on the normal side may usually be demonstrated by injecting the abnormal side while compressing the carotid artery in the neck on the normal side. Some of the difficulties encountered when vertebral arteriography is used for the localization of posterior fossa masses are discussed.

RESUMEN

Los cambios angiográficos causados por los tumores incluyen el estiramiento de los vasos, cambios en la circulación tumoral, el aumento de la velocidad circulatoria local, la disminución de la velocidad circulatoria local, una zona avascular y el desplazamiento de los vasos. Si todos estos signos tienen que ser apreciados, resulta importante la standardización de la cantidad de medio de contraste y de la velocidad de su inyección. Diez centímetros cúbicos del medio de contraste por segundo son suficientes para una inyección en la arteria carótida interna. Las series angiográficas deben cubrir totalmente las fases arteriales y venosas. Se define el triángulo de Silvio, formado por ramificaciones de la arteria cerebral media a la vez que se discute su importancia para la localización de las masas supratentoriales. En general los vasos sanguíneos se desplazan lejos de la lesión, y los más cercanos a la masa son los que experimentan los desplazamientos más marcados. Este dispositivo fundamental se ve modificado en los casos de hernia del cerebro, ya que ciertos desplazamientos son limitados o alterados por la hoz o el tentorio. Se describen las modificaciones causadas por los tumores frontales, parietales, occipitales, temporales y talámicos. Cuando los desplazamientos vasculares son relativamente leves puede resultar útil la comparación de los vasos de la región normal con los de la región afectada. Los primeros pueden hacerse observables por medio de una inyección dada en el lado afectado, a la vez que se oprime la arteria carótida, en el cuello del lado sano. Se discuten las dificultades encontradas al utilizarse la arteriografía vertebral para la localización de las masas de la fosa posterior.

RÉSUMÉ

Les changements angiographiques causés par des tumeurs incluent des élongements des vaisseaux, des changements de la circulation tumorale, augmentation de la vitesse circulatoire locale du sang, diminution de la vitesse de la circulation locale une zone avasculaire et déplacement des vaisseaux. Si tous les signes doivent être appreciés, il est important de standardiser la quantité du milieu de contraste et la vitesse de son injection. Dix centimètres cubes (10 cc) du milieu de contraste par seconde suffisent pour une injection de l'artère carotide interne. Les séries angiographiques doivent couvrir complètement les phases arterielles et veineuses. Le triangle de Sylvius formé par des branches de l'artère cerebrale moyenne est défini et son importance pour la localisation des masses supratentorielles est discutée. En géneral les vaisseaux sont déplacés loin de la lésion et les vaisseaux les plus près de la masse montrent les déplacements les plus marqués. Cette représentation fondamentale est changée en cas des herniations du cerveau, parce que certaines déplacements son limités ou modifiés par le falx et le tentorium. Les changements causés par les tumeurs frontales, pariétales, occipitales, temporales et thalamiques sont décrits. Quand les déplacements des vaisseaux sont relativement légers, il peut être avantageux de comparer les vaisseaux du côté affecté avec le côté normal. Les vaisseaux du côté normal peuvent ordinairement être demontrés par une injection du côté affecté pendant la compression de l'artère carotidienne dans le cou du côté normal. Quelques difficultés rencontrées quand l'arteriographie vértébrale est utilisée pour la localisation des masses de la fosse posterieure sont discutées.

ZUSAMMENFASSUNG

Die angiographischen durch Tumore verursachten Veränderungen umfassen Dehnung der Gefässe, Durchblutung des Tumors, örtliche Verzögerung der Durchblutungszeit, eine gefässarme Zone, und Verlagerung der Gefässe. Wenn all diese Zeichen erscheinen sollen, ist es wichtig die Geschwindigkeit und das Quantum des zu injezierenden Kontrastmittels festzusetzen. 10 cc Kontrastmittel per Sekunde ist ausreichend für eine Injektion in die Arteria carotis interna. Die Filmserien müssen die gesamte arterielle und venöse Phasen beinhalten. Das sylvische Dreieck, durch die Aeste der mittleren cerebralen Arterie gebildet ist festgesetzt, und seine Bedeutung in der Lokalisierung der supratentorialen Gebilden wird besprochen. Im allgemeinen sind die Gefässe von raumverdrängenden Prozessen verlagert, und die Gefässe die am nächsten zum Prozess liegen zeigen stärkste Verlagerung. Dieses grundlegende Verhalten aendert sich bei Hirnherniationen weil bestimmte Verlagerungen durch die Falx und das Tentorium begrenzt oder gemildert sind. Veränderungen durch frontale, parietale, occipitale, temporale und thalamische Tumore veranlasst, werden beschrieben. Wenn die Verlagerungen der Gefässe relativ gering sind kann ein Vergleich zwischen den Gefässen der normalen und angegriffenen Seite sehr behilflich sein. Die Gefässe der normalen Seite können gewöhnlich durch Injection der angegriffenen Seite gezeigt werden, während die Arteria carotis der normalen Seite im Hals comprimiert wird. Es werden verschiedene Schwierigkeiten besprochen die auftreten wenn Vertebralis-arteriographie zur Bestimmung der Prozesse der hinteren Schädelgrube verwendet wird.

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Radioisotope Detection of Brain Tumors

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INTRODUCTION

Understanding the role of isotopes in the detection of brain tumors involves several divergent disciplines. In a brief article such as this no serious attempt at a complete review of the subject can be made. I shall confine myself to those aspects of the problem which might interest the clinician considering undertaking this relatively new diagnostic technique.

Radioisotopes in tissue can be measured by detecting and counting the penetrating rays such substances emit. Of particular interest to the clinician are those isotopes emitting rays sufficiently penetrating (gamma rays) that they can reach the surface and emerge from a living organism as large as a human. After their emergence their number and direction of origin can be noted, allowing the construction of a map of the distribution of isotope within the body.

Early in the development of nuclear medicine advantage was taken of this possibility of measuring externally the amount of isotope within an organ. Greatest interest was shown in the uptake of iodine131 by the thyroid. By "looking" at the region of the neck containing the thyroid the amount of radioiodine present could be measured some hours after its administration. By restricting the region "seen" by the detector to a few millimeters and scanning back and forth over the region of the gland a crude map of iodine distribution could be constructed and local abnormalities of iodine uptake determined [3].

All of these results with the thyroid were fairly easily obtainable with simple equipment because a large proportion of the administered iodine concentrated in the gland. A large concentration of isotope allows many points to be incorporated into the distribution map in a short scan period. In the region of the thyroid virtually all of the iodine was in the thyroid tissue, thereby allowing sharp demarcation from other tissues.

When this general plan of administering an isotope and later mapping its distribution in the body was applied to other isotopes and other organs it became evident that it was truly useful only if a large proportion of the material concentrated in the organ of interest. To the present time this high local concentration has been achieved to a clinically useful degree only in thyroid, liver and kidneys. Much of the current research in nuclear medicine is directed at obtaining high selective tissue concentration in other organs.

The brain is particularly resistant to concentration of all known labeled substances of clinical interest. This is probably another expression of the phenomenon of the blood brain barrier. When a substance is administered intravenously it is carried into the brain by the blood but the low permeability of brain capillaries keeps the material within the blood. Most substances will achieve a much lower brain tissue concentration (outside the blood compartment) than in other organs. If the entire body distribution were mapped after administration of most isotopes the brain would be seeen as an area relatively free of isotopes. One advantage realized in detecting brain isotopes is the fortunate location of the brain well away from other large organs with which it might be confused. Nevertheless it is surrounded by scalp, skull, meninges and some muscle, all of which behave like other non-neural tissue. As a consequence the brain has a "halo" whose capillaries are relatively permeable. Below the level of the cranial floor are sub occipital and facial tissues. For this reason the brain tissue along the floor of the cranial cavity, in the sella turcica and posterior fossa are more or less obscured by these adjacent soft tissues.

In 1947 Moore [14] observed that fluorescein injected intravenously appeared in brain tumors in sufficiently high concentration relative to normal brain that the tumor was quite visible when exposed to ultraviolet light. In addition to the use of his technique as a quick and useful means of identifying tumor tissue at operation, it occurred to that author that fluorescein might be labeled with a radioactive tag greatly facilitating the ability to measure the fluorescein content not only *in vitro* but *in vivo*. Fluorescein was easily labeled with131 and subsequent studies showed that the gamma emission of this material was capable of indicating the presence of a brain tumor in living human brain through an intact cranium. Tumors could be "seen" as a region of high radioactivity against a low background of normal brain. In the sixteen years since that observation development of the technique of isotope detection of brain tumors has centered about two factors: more efficient detection systems and more suitable isotopes.

Technique and Detection Systems

To perform a brain scan with a currently popular tracer (Hg203 labeled neohydrin) the patient is given an appointment to be scanned late in the work day such as 2 P.M. At about 9 A.M. (four to five hours before scanning) he is given intravenously a dose of about ten microcuries per kilogram body weight. This is given in any convenient vein and causes only the pain of vein puncture. There is, of course, no subjective effect of the radioactivity. This simplicity and freedom from hazard or discomfort have spurred the interest of researchers through the years.

It remains only to map the brain distribution of isotope four to five hours later. The patient is taken to the scanning room at 2 P.M. and placed in position under the scanning detector. His head is firmly fixed in position. It must remain fixed for at least twenty minutes during the scan. This, of course, precludes the study of patients unable to cooperate by maintaining one position for a prolonged period.

It is vital at this point that the clinician has some understantindg of the special apparatus used in isotope scanning. The task of brain tumor detection equipment is extremely difficult. The tissue concentration of isotope is very low despite large administered doses. Thus the maximum possible efficiency must be realized, utilizing as many of the emitted rays as possible. We are always limited by the time we can reasonably expect the patient to remain in a fixed position.

Initially in the development of head scanners a detector was placed over a succession of regions of the head and a count made for several minutes at each site. This was reasonably successful but the resulting picture that could be constructed was very crude (Figure 1A).

If the region seen by the detector is restricted by a focused arrangement of shielding we can demarcate the site of origin fairly accurately (Figure 1B). However, in gaining this precision of location we have sacrificed a great deal of sensitivity since at any one time only the isotope at the focal point will be registered (Figure 2). As this focused collimator is scanned back and forth over the head for perhaps an hour it is evident that only an incredibly small proportion of the rays emitted from the brain during that hours is actually detected and incorporated into our distribution map. The higher the spatial resolution obtained the lower this efficiency becomes.

Several commercial scanners are now available which function in this way by moving a focused detector slowly over the region of interest, producing a series of marks mechanically or photographically reproducing the isotope distribution in the region.

A technique introduced by Wrenn *et al*[21] and developed by Brownell and Sweet[7] offered certain advantages. They utilized a unique form of radioactive decay (positron emission) which results in the creation of two identical gamma rays originating at a common point in space precisely simultaneously and proceeding in precisely opposite directions. By placing

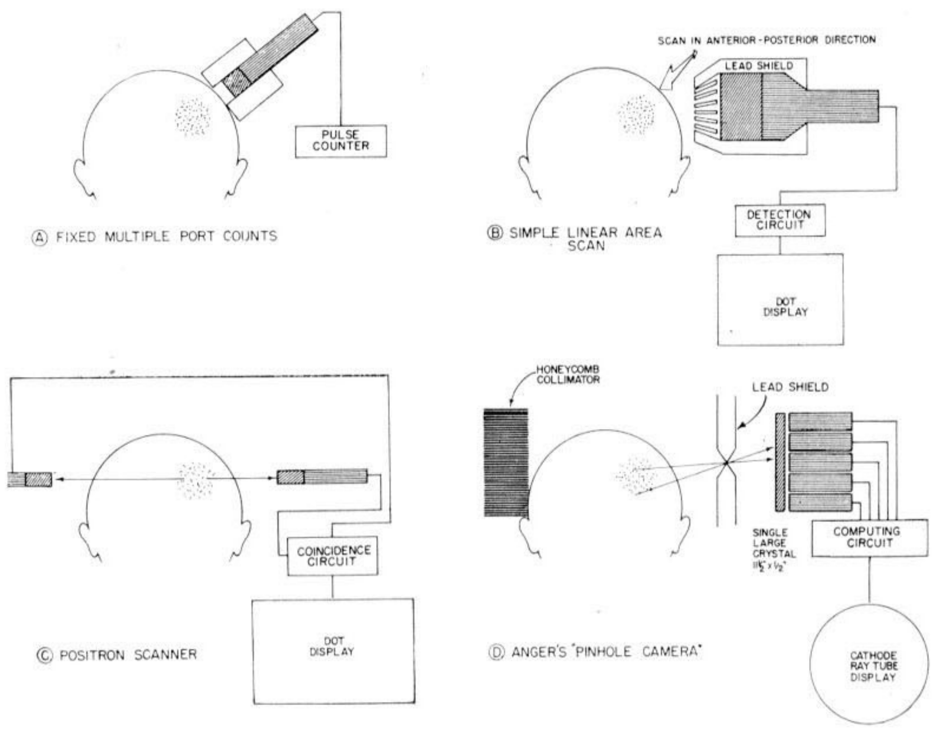

Fig. 1. — *Four basic schemes of mapping isotope distribution. "B" is the system in common use. In system "D" the "honeycomb" collimator shown to the left of the head could be substituted for the pinhole. When interposed between head and crystal it can form in the crystal an image of isotope distribution in brain which is somewhat less geometrically distorted than that formed by the pinhole.*

two detection crystals on opposite sides of the head it is possible to restrict the region of sensitivity to a cylindrical space connecting the two (Figure 1C). A pair of rays originating within this region will sometimes be directed so that each ray will strike one of the crystals. The electronic circuitry to which the detector output is fed is arranged so that an event is recorded only when a pulse appears simultaneously from both crystal detectors. This will occur rarely from rays originating outside the cylindrical region between the crystals. This method is restricted by the relatively few available isotopes.

Newer developments have sought an increased efficiency of ray utilization and improved spatial resolution. Of considerable interest is the "gamma ray pinhole camera" of Anger (Figure 1D). If one could place a piece of film near the head and create an aperture in an otherwise opaque screen between the film and the head it would be possible to form an inverted image of the distribution of isotope in the head just as in the familiar visible light pinhole camera. This is not practical because any rays sufficiently penetrating to reach the surface of the head will most likely pass on through a photographic emulsion without interacting with it. It therefore would be exceedingly inefficient. Anger has replaced the film in such a pinhole camera arrangement with a one-half inch thick sodium iodide crystal.

A small but significant percentage of gamma rays entering this thickness of crystal will interact with it and produce a faint flash of light. By an ingenious arrangement of photomultiplier tubes and electronic circuitry this flash is detected and its position within the crystal determined. A flash of light bright enough to see with the unaided eye is caused to appear on the face of a cathode ray tube at a position corresponding to the original very faint scintillation in the crystal. This tube is then photographed during an interval of perhaps one minute and each flash is incorporated into a final accumulated image.

Several advantages are realized with such an arrangement. The system is quite efficient and more of the gamma rays are utilized than in mechanical scanning. A great advantage is the simultaneous build-up of the entire image during the "scan" period. In mechanical scanners several minutes (perhaps as long as an hour) may elapse between the beginning of a scan on one edge of an area and the end of the scan on the far edge of the area. This requires that the concentration of isotope remains reasonably constant in the tissue during the scanning period. A device which builds up the entire image simultaneously can still be used when very short-lived isotopes are used. As noted later such short-lived isotopes have considerable merit and will probably become widely used.

In this connection it may be of interest to study the distribution of substances which physically decay or wash rapidly out of the brain in a few minutes but achieve very high initial levels.

The great disadvantage at present of such devices as the gamma ray pinhole camera is their great complexity. This probable will become less of an obstacle as they become commercially available and electronic reliability improves.

The true obstacle to the development of such a device as the pinhole camera is the failure of general recognition by the clinical community that such an expensive device is necessary for patient management.

Choice of Isotopes

There is still not a general agreement on the best isotope for brain tumor localization because of the multitude of factors to be considered.

The most important of these factors are:

1. Patient radiation should be minimized.
2. An attempt shoud be made to achieve a tumor concentration substantially different from surrounding brain.
3. The gamma radiation must be sufficiently penetrating to emerge from the depths of the head but not so penetrating that it is impossible to construct a practical shield to restrict the direction of sensitivity of the detector.

Minimizing Patient Radiation

So little of any administered isotope goes to brain that a dose is required which is much larger than needed for most other tests. As a consequence the dose usually is pushed up to the ethical limits of the physician administering the test. Because of this need to use the largest possible dose the radiation absorbed by the patient is of great importance.

The radiation suffered by the patient's tissues from the intravenous injection of a given dose of radioactivity can vary widely depending upon the type of radiation emitted, the physical rate of decay of the radioactive material, the distribution of the material in the body and its rate of excretion into the environment. An attempt is made to juggle these factors trying to render the isotope most useful for the study to be undertaken and to minimize radiation to the patient. The isotope chosen as a tracer substance will determine the type of radiation emitted and the molecule into which it is incorporated will determine its distribution and fate within the body.

Most radioisotopes of clinical interest emit some combination of beta and gamma radiation. Some emit only gamma rays. The beta radiation emitted causes the bulk of the patient radiation so that the same amount of a pure gamma-emitter results in much less patient radiation than the same dose of a mixed beta and gamma emitter. Thus the same dose of Hg197 (a non-beta emitter with a gamma at 0.077 MEV) will radiate the patient much less than the same dose of Hg203 (a beta and gamma emitter). Considerable interest is being shown currently in Hg197 as a substitute

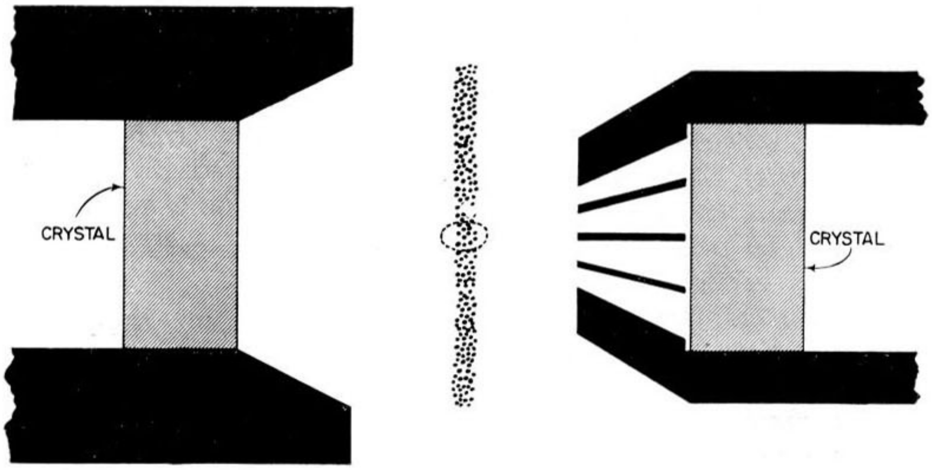

Fig. 2. — To demonstrate the loss of count inherent in focused collimation. The crystal on the left "sees" the entire field of distribution of isotope in the middle. On the right a focused collimator restricts the area seen and thus will count only the isotope in the small elliptical region outlined. As this area is further restricted obtaining better localization count is lost proportionately.

for Hg203 for brain scanning. It removes the most serious objection to Hg203 neohydrin — the high kidney dose absorbed. The half-life of Hg197 (65 hours) is short compared to Hg203 (45 days). The absence of nuclear beta emission further reduces the dose absorbed.

Patient radiation depends also on the rate at which the material itself decays and its rate of excretion from the body. Thus an extremely large dose of a short half-life substance such as Ba137 (half-life 2.6 minutes) may be administered with little danger. A very large dose of a rapidly excreted dosage form such as iodine131 hippurate can similarly be given safely because it can be entirely voided within a few hours.

Until recently little attention was given to very short-lived isotopes since they would decay away between manufacture and delivery. Most medical work has been done with isotopes of intermediate half-life such as iodine131 (8.3 day half-life). This makes shipping convenient and allows the material to be kept on hand a week or two without decaying away prohibitively. Considerable interest is now being shown in the possibility of obtaining in the clinical laboratory short-lived isotopes which result from the decay of longer-lived isotopes. These shorter-lived materials are extracted as they are formed. Since they are immediately available for injection very short-lived materials can be used, even those with half-lives of a few minutes. The simple device from which the desired substance is withdrawn is appropriately called a "cow". The problems with these devices are the difficulties in obtaining the isotope in a desired chemical form, sterile and pyrogen free.

Very short-lived isotopes must, of course, be used with scanning systems which can function in the presence of a rapidly falling count rate. Most commercial mechanical scanners are not suitable for this purpose.

For positron scanning As74, Zn65 and Cu64 have been used. Some of these have long half-lives and are very slowly excreted from the body. They are, therefore, undesirable from a radiation standpoint.

Anger *et al* [1] have recently described the use for brain scanning of gallium68, a positron emitter with a half-life of 68 minutes administered bound with a chelating agent as described by Gleason [10] and Greene and Tucker [11].

Ratio of Tumor to Brain Tissue Concentration

The first substance to be studied extensively for tumor uptake was iodine131 fluorescein. It was relatively permeable into tumors compared with normal brain but was very rapidly removed from the blood by the liver. This rapidly falling blood level did not offer much time for permeation into tumor tissue and measurements extending over a period of time were complicated since the amount of isotope in the brain was changing rapidly.

Interest then centered for several years on iodinated human serum albumin. The blood level fell very slowly and it was more permeable into most tumors than into normal brain. It suffered, however, from the disadvantage that the blood concentration remained high for several days and the isotope in the blood of the brain offered a high background level against which the tumor must be visible. This high persisting blood level may partially account for the visualization of some tumors by virtue of their relatively high blood content. Many workers still favor this substance [8].

More recently mercury203 labeled neohydrin (chlormerodrin) has been found to be more satisfactory [5, 6]. About four hours after administration the blood concentration has fallen to about 15 percent of the original level. It is very impermeable into normal brain but more permeable into most tumors. If the brain is scanned about four hours after administration the blood level is quite low so the tissue concentration is seen against a relatively clear background. The gamma radiation of mercury203 has a very desirable intermediate penetrating power (somewhat less than iodine131), making its localization more precise as noted below.

Neohydrin has a great disadvantage in that about a fifth of the entire dose is quite permanently bound in the kidney where it remains for many months decaying with a half-life of 45 days. The kidneys consequently receive a rather large radiation dosage. Attempts at reducing renal fixation have been made by the preliminary administration of a relatively large amount of non-radioactive neohydrin which apparently competes with the radioactive material for the available sulfhydryl complexes in the renal tubules.

In addition to those already mentioned many other substances have been evaluated such as K42 [13], polyvinylpyrrolidone [19], octoiodofluorescein [20] etc., each seeking more favorable tumor to brain concentration ratios. From these evaluations it would seem many substances possibly are useful in that they appear in tumors in higher concentration than in brain. Too little data exists, however, concerning the quantitation of tumor versus brain concentrations. Some work has been done [4, 9, 15, 17, 18] determining levels postmortem and at operation but this has obvious limitations since the dose must be administered shortly before surgery or before death and the results so obtained may well not be representative of the usual clinical situation. The tumor to brain ratio will vary as a function of time after injection and also probably varies with the evolution of the tumor and its cell type.

It is evident, however, that many substances will appear in tumor tissue in concentrations in the range of 5 to 50 times that found in normal brain. Most meningiomas, glioblastomas and metastases will show concentrations in the range of 10 to 30 times normal brain while low grade astrocytomas commonly show very little more uptake, perhaps 1 to 5 times normal brain. It must be kept in mind that these ratios are largely dependent upon the low uptake of the surrounding normal brain tissue, and not to the specific concentrating ability of the tumors.

To better understand the permeation of labeled substances into brain, we have attempted to develop a technique for quantitative brain tissue uptake of a wide range of gamma-emitters [16]. We have a detection system which sees the entire upper half of the head with uniform efficiency above the line roughly paralleling the floor of the cranial cavity on each of the outlines of Figure 3. This allows the measurement, after adequate standardization with a phantom, of the total cranial isotope content. After its intravenous injection the antecubital venous blood concentration is followed down as it is excreted or otherwise removed from the blood and the total cranial content is simultaneously monitored. Initially all of the cranial isotope is assumed to be in the blood of the brain. Beginning at two minutes the brain and blood levels are arbitrarily equated at 100 %. As the blood level falls the cranial level also falls but less rapidly since some of the material will have diffused out of the blood into the extravascular compartment. By subtracting the blood isotope from the total cranial content a curve can be constructed which represents the amount of isotope in the cranial portion of the head but not in the cranial blood pool.

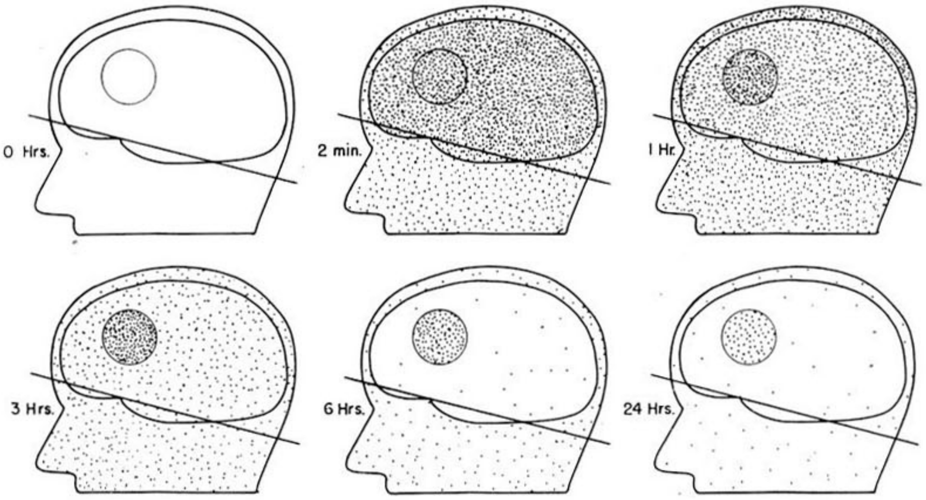

Fig. 3. — *Showing very diagrammatically the washout of neohydrin from a frontal cerebral tumor. In the period from about 3 to 8 hours the tumor will contain a high concentration of isotope relative to the surrounding brain. When scanned this "hot spot" can be demonstrated. The optimum time for scanning will vary somewhat for different tumors.*

Although we have applied this technique to the entire cranium it would be equally aplicable to local regions known to contain a tumor. We have found most tumors to be detectable (although not localizable) by this means even though any tumor effect is diluted by the normal tissue present (Figure 3). The technique requires extremely small doses (5-10 microcuries) and relatively simple equipment. By sacrificing localization we have achieved an extreme increase in efficiency of utilization of gamma rays.

Penetration of Gamma Radiation

Only those isotopes emitting gamma rays sufficiently penetrating to escape from the depths of the brain are of clinical value in tumor localization. Their penetrating properties can be deduced from their energy level. Those of less than about 50 kilovolt energy level are of little interest in the brain because the scalp and other superficial tissues will appear very prominent and the skull will absorb much of the radiation originating within.

Rays of more than about 500 kilovolt energy level become very difficult to collimate because they penetrate the thin septa in focused collimators. Crystals are also less efficient at higher energies because they too are more often penetrated without interacting with the ray. All gamma rays originating from positron emission are at 510 kilovolts but here focused collimators are not depended upon for localization.

For these reasons most isotopes considered for brain scanning have gamma rays with energies between 75 and 500 kilovolts.

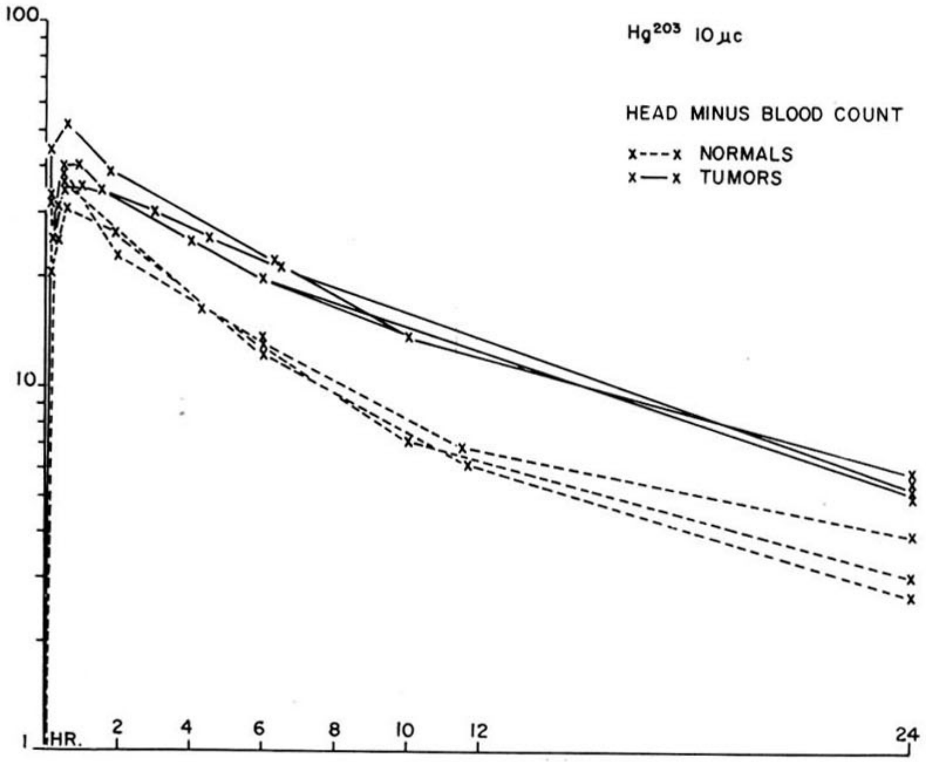

Fig. 4. — *From Figure 3 it is to be expected that the tumor will cause the tissue isotope content to be raised above that to be expected were the tumor not present. Here three tumors (two glioblastomas and one bronchogenic metastasis) are compared to three normals. These particular tumors were quite advanced but we have found most of our first 25 tumors to be differentiable from our control cases by this technique.*

COMMENT

Isotopes undoubtedly offer a clinically useful technique in the early detection of brain tumors. As a part of the total clinical picture it is certainly as useful as the electroencephalogram. Even the more elaborate scanning equipment now available costs only about as much as an eight channel electroencephalograph.

Currently available equipment has an

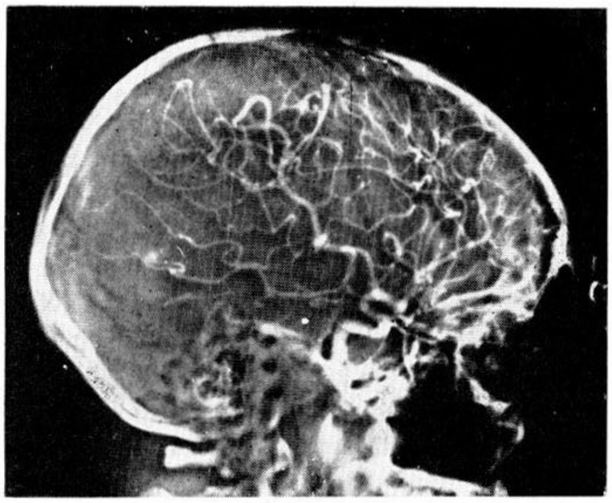

Fig. 5 a

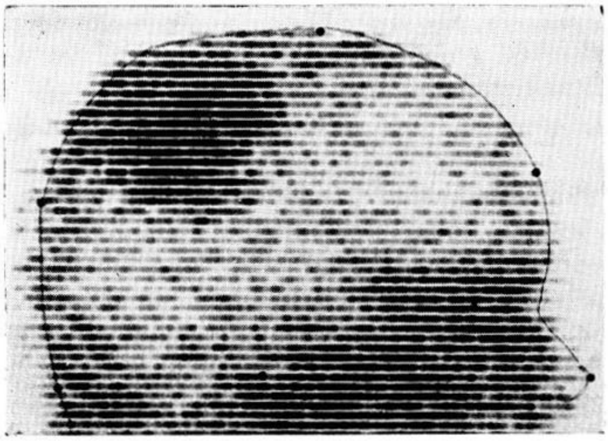

Fig. 5 c

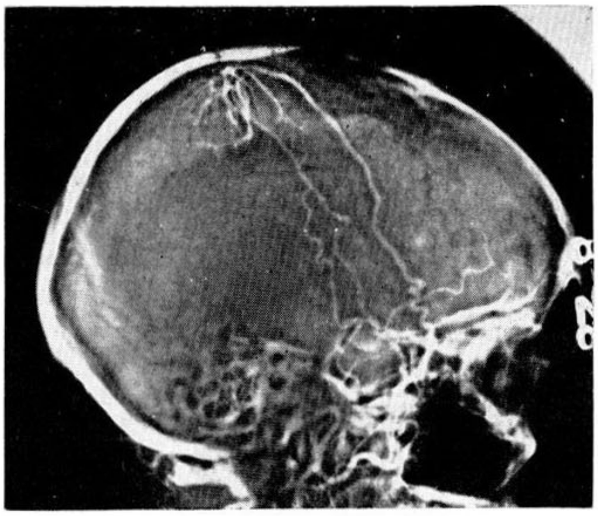

Fig. 5 b

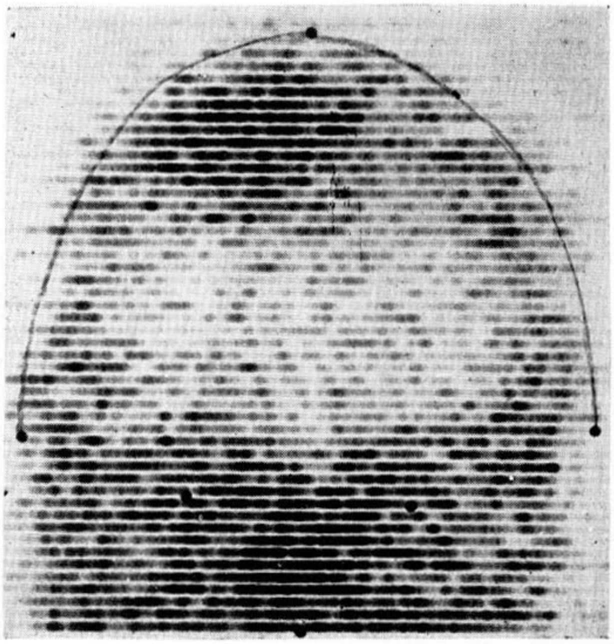

Fig. 5 d

Fig. 5, *indicating the different form of information provided by an isotope scan versus a carotid angiogram. The patient is a 34 year old male with a surgically verified large parasagittal meniogioma. — 5a, is an internal carotid injection indicating displacement and probable excessive blood supply to the region of the tumor but with little filling of the tumor itself. — 5b, an external carotid injection indicating filling of the tumor through scalp and meningeal branches. — 5c, is a brain scan 3 hours after the administration of 1 millicurie of Hg197 chlormerodrin. The localization and size of the region of increased isotope retention can be approximated. — 5d. The scan in the coronal plane indicates the increased uptake to be in the right parasagittal region. The angiogram gives specific information about blood supply and thus, in this case, its probable tissue type as well as accurate localization. This patient's workup could logically have included the relatively atraumatic scan first, with later supplementation by the angiogram since they supply information about two quite different aspects of the tumor.*

admittedly poor spatial resolution but it is questionable whether extreme resolution is required. The maximum possible resolution is probably ultimately limited by our inability to fix the head absolutely during a long scan period although this is not important with existing equipment where the resolution is only one to two centimeters.

Brain tumor scanning has not developed

as rapidly as it might have for several reasons. Radioisotope scanning as well as other "atomic" techniques generated a considerable ambivalence in the medical public. Although appreciated as a very useful tool it requires a knowledge of a new field quite alien to many clinicians. To use isotopes intelligently requires a practical knowledge of nuclear medicine, a license to handle radioactive materials and facilities to order and store isotopes. These all are functions carried out by any nuclear medicine department and by an increasing number of practitioners unassociated with any organized department.

It was further tainted by widespread professional and lay preoccupation with the hazards of nuclear radiation. It is vital to recognize that the radiation suffered by the body is lower from most diagnostic radioisotope tests than that received during a single radiographic chest film exposure and very much lower than from a gastrointestinal series or other fluoroscopic technique.

Brain scanning in particular has been hampered by a failure to settle on a single technique largely due to the patient radiation encountered with al current approaches.

Most clinicians prefer to go directly to the angiogram in suspect cases. By so doing they remain on familiar ground combining surgery and radiology, obtaining a rather definitive answer quickly without the delay inherent in isotope studies.

In the early 1950's when brain scanning was in its infancy carotid angiography was also developing. Of particular importance in its growth were the gradual shift from open carotid arteriopuncture to the simpler percutaneous puncture and the replacement of insoluble (and radioactive) thorium dioxide by soluble iodized salts culminating in the current diatrizoates and related compounds which are very non-irritating and very safe to inject. In addition, the development of rapid serial techniques has greatly enhanced the usefulness of cerebral angiography, allowing a detailed analysis not only of regional vascular architecture but of the rates of filling of each region [12]. With the serial angiogram the clinician has a high-definition picture of the spatial and temporal distribution of momentarily opacified blood in the brain that tells him a great deal about brain morphology and blood supply.

The angiogram is, however, a complex and traumatic procedure which ideally should be carried out only by skilled angiographers. When thus performed it is very safe but when carried out as an occasional procedure by relatively unskilled angiographers it not only loses much of its diagnostic value but can become relatively hazardous.

Since angiography and isotope scans assess quite different aspects of brain structure and function it is difficult to compare them. However, if the clinician is satisfied with the crude detail inherent in isotope scans this approach will probably detect about as many tumors as angiography. Because of these factors there seems to be a definite place for isotope scanning for brain tumor screening where for some reason a carotid angiogram is unwarranted. In the face of a suggestive scan, arrangements can be made for a more definitive workup which might include serial angiography or an air study.

One example of the usefulness of brain scanning might be encountered in the management of a patient in poor general condition in whom cerebral metastasis is suspected. If more than one site of brain uptake could clearly be demonstrated by isotope scanning brain metastasis might be presumed, sparing the patient the discomfort and hazard of carotid angiography. This information could be obtained with no discomfort whatever and at no risk since scanning is completely painless and atraumatic other than the slight radiation hazard to the patient.

At the present state of scanning technology patient radiation is rather high by very conservative standards. Recent innovations such as Hg197 neohydrin may largely have solved that problem. It is not clear at present how much radiation is "acceptable". All organisms are subjected to an inevitable background radiation from cosmic rays and naturally occurring radioisotopes. Most of the isotope tests now carried out do not apreciably increase this accumulation from natural sources. The very conservative, however, argue that *any* additional radiation is too much. With further development of instruments and more desirable isotopes useful pictures should be obtainable with radiation dosage acceptable to even the most conservative critics.

The development of new instrumentation is, however, very costly. Engineering firms profit from the sale of instruments, not directly from their development. If the clinician expresses sufficient interest in these devices, further development will be stimulated. We shall then be closer to fulfilling in clinical neurology the great promise which nuclear medicine offers to all clinical disciplines.

SUMMARY

1. A general review of the development and present status of brain tumor scanning is presented. 2. Tumors are detectable because many labeled compounds will diffuse into tumors from the blood more readily than into the surrounding brain. 3. Tumor scanning seems a useful part of the clinical armamentarium but must be assigned a realistic role in the overall clinical workup. 4. It is completely painless and atraumatic. 5. The only hazard associated with this technique is the minimal radiation absorbed by the patient.

RESUMEN

1. Se presenta un análisis general del desarrollo y estado actual del "scanning" del tumor cerebral. 2. Los tumores son localizables porque varios compuestos marcados se difunden en los tumores desde la sangre más rápidamente que en la masa cerebral colindante. 3. El "scanning" del tumor parece ser un elemento útil entre los instrumentos de uso clínico; pero debe ser usado en la clínica con criterio realista. 4. Es absolutamente indoloro y atraumático. 5. El único peligro asociado a esta técnica es la radiación mínima que el paciente absorbe.

RÉSUMÉ

1. On présente une vue générale du développement et de l'état présent du "scanning" de la tumeur cérébrale. 2. Les tumeurs peuvent être localisées parce que beaucoup de substances marqués se propageront du sang aux tumeurs plus rapidement qu'à la masse cérébrale voisine. 3. Le "scanning" l'une tumeur est utile comme instrument clinique, mais on doit lui donner un rôle réaliste dans le travail clinique d'ensemble 4. Cela ne provoque aucune douleur et c'est atraumatique. 5. Le seul danger associé à cette téchnique est la radiation minimale absorbée par le patient.

ZUSAMMENFASSUNG

1. Es wird eine allgemeine Uebersicht ueber die Entwicklung und den heutigen Stand der Hirntumordiagnostik mit radioaktiven Isotopen gegeben. 2. Die Geschwuelste sind erkennbar, weil viele mit Isotopen "markierte" chemische Verbindun-

gen schneller vom Blut in die Geschwuelste hinein diffundieren als in die sie umgebenden Gehirnmasse. 3. Die Isotopentumordiagnostik scheint eine nuetzliche Erweiterung des klinischen Ruestzeuges zu sein; aber es muss ihr eine realistische Rolle bei der allgemeinen klinischen Verwertung zugewiesen werden. 4. Diese Methode ist vollkommen schmerzlos und nicht traumatisch. 5. Das einzige mit dieser Technik verbundene Risiko besteht in der minimalen vom Patienten absorbierten Radiation.

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Pneumoencephalography in Brain Tumors

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INTRODUCTION

It is not impossible to condense a 15-year experience on pneumoencephalography within a paper in which the main goal is to draw only general outlinings on the subject, provided one accordingly chooses the proper subjects to discuss, relinquishing any discussion on those aspects which must be considered as foregrounds and on which we would advise to consult our previous papers and those of our school at the Serafimer-lazzarettet. At the present time it will suffice to state that our further experience has more than ever convinced us that fractional air study is the best technique by far in cases of brain tumors. There is no doubt that ventriculography still plays an important role among the Neuroradiological techniques; however, in our Department, in the last three years it has never been carried out as first examination, but only when fractional encephalography had failed to make a warranted diagnosis. Table 1 shows how frequently the two examinations have been carried out.

We shall not entertain in any technical detail either. Usually, as previously stated by Lindgren, we let the examination be, so to speak, its own performer, for the Neuroradiologist carries it out according to the information acquired from the initial films without following the rules of a bounding routine. However, in our Department, the encephalographic techniques have become more refined and more enriched by means of new technical advancements among which the utilization of the image intensifier with television control; the sumministration of urea according to a personal technique of ours and the amount and rate of introducing the contrast medium and of withdrawing (or not withdrawing) cerebrospinal fluid. In so doing, the examination time has been markedly shortened especially that part of it performed with the patient in sitting position, thus decreasing the risks of the examination and consequently improving its tolerability. It is now for us a rule of paramount importance in the encephalographic technique to keep a patient as little as possible in the sitting position especially when general anesthesia is required. This is being supported by the first results of our clinico-experimental researches.

Diagnostic importance of fractional encephalography

This subject can be viewed and discussed from many sides: that of a competition between encephalography and ventriculography as already mentioned above; the role played by the former in the diagnosis of location and above all, of relationship of a tumor to the brain by stating whether a lesion is intra- or extracerebral; its indication in a specific group of tumors:

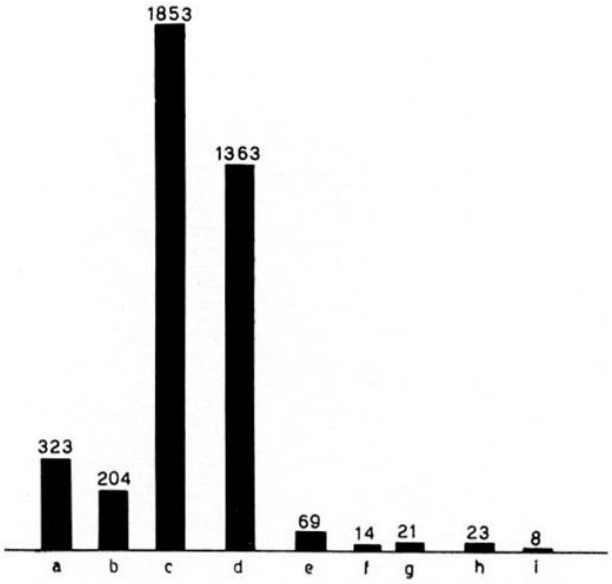


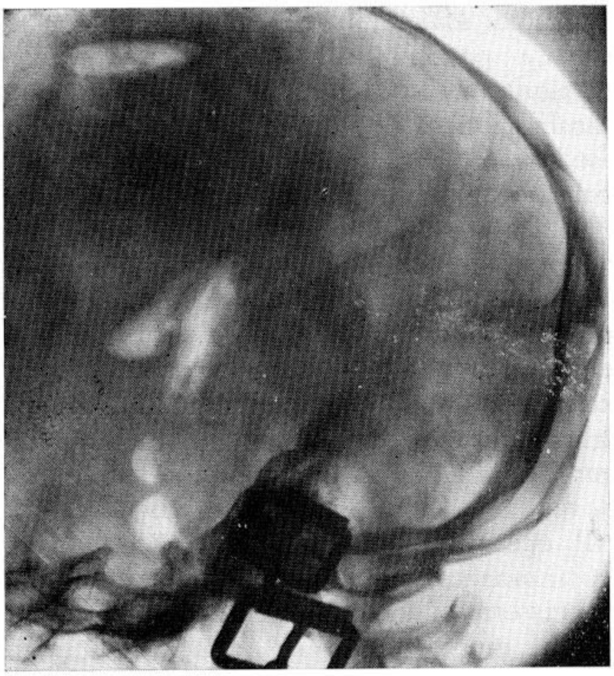
Fig. 1. — *Examination by means of contrast of cerebral exploration effected in the Department of Neuroradiology of the Ospedale Maggiore, from November 1st., 1961 to June 7, 1694. a) vertebral arteriography; b) external carotid arteriography; c) internal or common carotid arteriography; d) fractioned encephalography; h) gaseous ventricolography.*

suprasellar ones, of the posterior fossa, etc., the rate of filling of the ventricular system, etc. The editors of this Journal have kindly invited us to write this paper and we have interpreted their invitation as their desire to introduce the numerous physicians interested in the diseases of the Nervous System, to a general picture on the actual possibilities of pneumoencephalography and therefore we have tried to condense the principal features of the diagnostic value of encephalography in brain tumors, classified according to their location.

Posterior Fossa Tumors:

In the tumors of the cerebello-pontine angle or of the clivus, the main diagnostic problem is to establish the relationship of the lesion to the brain by pointing out whether it is extracerebral or not and thus trying to make, in the majority of the cases, a pathological diagnosis as well. Fractional air study is, in our opinion, the examination of choice, for the diagnosis is based upon the outlining of the cisterns. Both extracerebral and intracerebral tumors will displace the aqueduct and the fourth ventricle in the same way; that is a displacement upward, backward and to the opposite side; however the cisterns will behave differently: a large cerebral tumor extending to the inferior portion of the right lateral peduncle will displace the fourth ventricle posteriorly, superiorly and to the left side. The same displacement will occur in a case of a right acoustic neurinoma. However in the former case the cistern of the cerebello-pontine angle will be either normal or compressed from above and from the midline outward, whereas in the case of a neurinoma the cistern will be lifted and it will show a typical deformation. Even more typical is the case of midline tumors: a meningioma of the clivus will displace the fourth ventricle posteriorly altering the contour of its floor with a concavity open anteriorly and downward due to an indirect compression of the pons, in which the dilatation of the ventricular system may occur more often. However there are no doubts as to the differential diagnosis for the pontine cistern will appear completely different: in the case of a meningioma of the clivus (and/or of any other extracerebral tumor) it will be compressed and shifted backward; in a pontine glioma it will be either normal or irregular and shifted anteriorly. In the tumors of the anterior portion of the posterior fossa the ventricular system is usually easily filled, and the films can be interpreted without unduly difficulty, however a diagnosis can be also made by studying the subarachnoid spaces alone. In the tumors of the posterior portion of the posterior fossa a diagnosis can easily and accurately be made only when the fourth ventricle and the aqueduct are visualized, and consequently displaced anteriorly and/or towards the opposite side.

Unfortunately their filling does not occur but rarely, making the diagnosis rather in-



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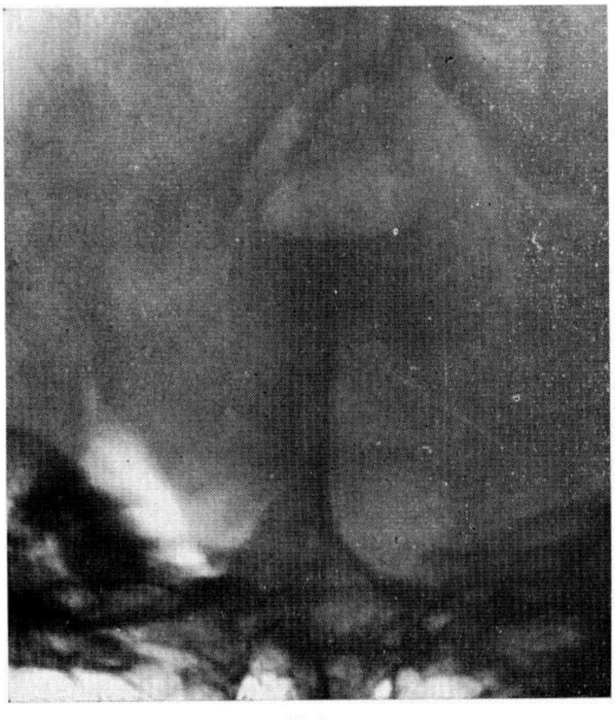

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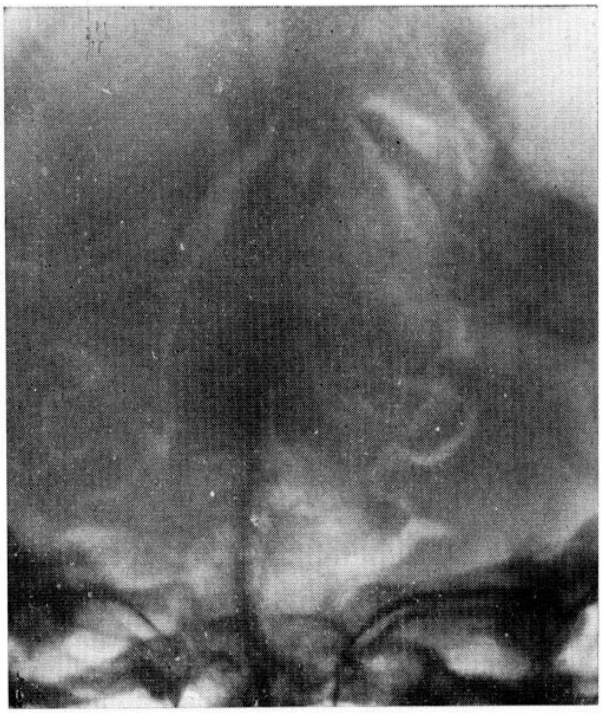
daginous. On the other hand the outlining of the cisterns will always make it possible to state that the lesion is located within the posterior portion of the posterior fossa, however it will seldom show the side of a cerebellar lobe tumor or the midline position of a tumor whether of the fourth ventricle or of the vermis.



2 c

Fig. 2. - *a, b and c.* — *Fractioned encephalography in a case of cerebral astrocytoma verified on the left side. The pontine cistern is considerably pushed against the clivus and the Galen vein cistern, and substantially lifted and pushed forward to the level of the inferior quadrigeminal plates; the air underneath the tentorium shows that same is lifted. These signs demonstrate the presence of a marked hypertension in the posterior part of the posterior fossa (a). On the left side the ponto-cerebellar angle cistern (b) and the inferior portion of the circumpeduncolar cistern (c) are not visualized, thus showing that the lesion is situated in the left cerebellar hemisphere.*

As opposed to the tumors of the anterior portion of the posterior fossa, in the cerebellar tumors the diagnosis is based upon indirect signs. In the former ones the site of the tumor —cerebello-pontine angle ou prepeduncular space— is clearly visible by the distortion of the cisterns, whereas in the cerebellar tumors this does not occur, for the cerebellum is not visible. Therefore the diagnosis can be established only indirectly, i.e. through the distortions of the brain stem and above all of the pons, displaced anteriorly and/or towards the op-

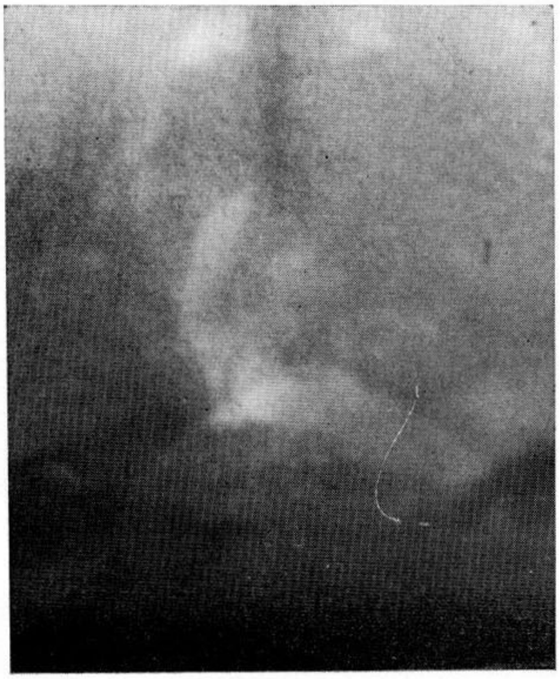


Fig. 3. — *Fractioned encephalography in a case of left cerebellar abscess. The cerebellar vallecula is displaced to the right.*

posite side. Its forward displacement is clearly shown by the typical appearance of the pontine cistern with its middle portion markedly pushed forward and compressed from behind determining an accentuation of its posterior concavity towards the anterior wall of the pons (fig. 2). This is an absolutely pathognomonic sign of a tumor of the posterior portion of the posterior fossa and it is very often associated with a filling defect of the extracerebellar portion of the cisterna magna, indicating a herniation of the cerebellar tonsils.

We have already stated that the accurate localization of a cerebellar lobe tumor (right, left or midline) may be difficult if there is no filling of the ventricular system.

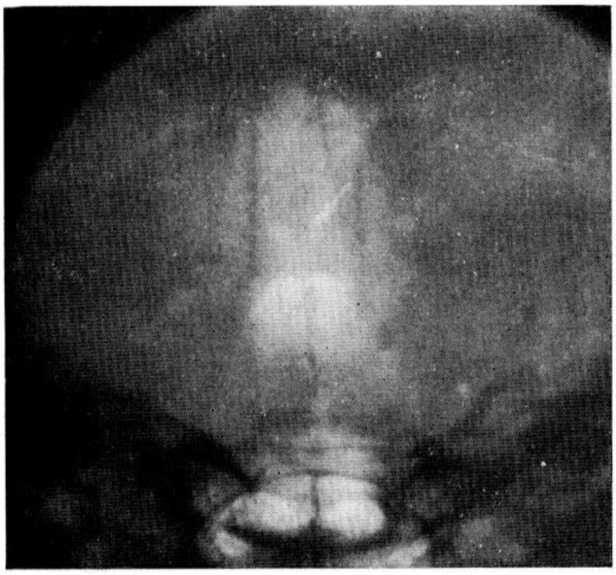
However (figs. 3 and 4) few other small signs can give some lead towards a more accurate diagnosis: a flattening or a lack of filling of one of the lateral recesses of the interpeduncular cisterna ambiens on one side; a marked assymmetry of the roof of the Cisterna of Galen, demonstrating that the transtentorial herniation of the posterior fossa structure is more prevalent on one side; a deviation or tilting of the anterior portion of the cisterna magna, cerebellar vallecula.

It must be emphasized that all these structures mainly because of their scanty visualization caused by the hypertension within the posterior fossa. As opposed to the hemispheral tumors, in these cases the sumministration of urea seldom causes the ventricular system to fill, however its use may still be advantageous as an indirect sign: if the fourth ventricle shows no filling even after urea, then the stenosis of the regular pathways between subarachnoid spaces and ventricular system may be stated to be caused directly by the tumor and not be the edema as in the cerebellar lobe tumors. The location of the space-occupying lesion is then to be placed near the midline.

When a tumor is located within the fourth ventricle, this is usually more or less completely visualized. If necessary, a ventriculography may be in order. We shall recall here the criterion of differential diagnosis between an intraventricular tumor and a tumor invading the fourth ventricle secondarily; in the former case the ventricle is distorted and "filled in" by the lesion, but not displaced; whereas in the latter one it is distorted and displaced.

An intracerebellar hemispheral tumor cannot be differentiated from an extracerebellar tumor, for instance a meningioma of the tentorium, on a pneumoencephalographic basis only. The meningiomas of the falcotentorial junction are the only exception.

Their dural attachment is located in proximity of the posterior surface of the incisura tentorial. There does exist a pathognomonic sign described by us together with Castellano: the straightening of the aqueduct. For this reason, when a tumor of this nature is suspected and encephalography has failed to fill the ventricular system, then ventriculography is mandatory in order to achieve a differential dignosis of paramount importance between meningiomas of the falcotentorial junction which are operable, and gliomas of the pineal region which are not.



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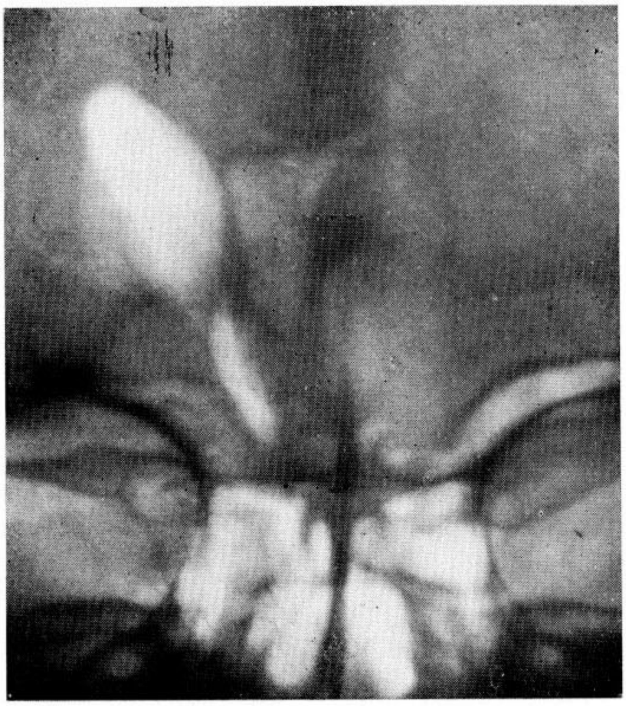

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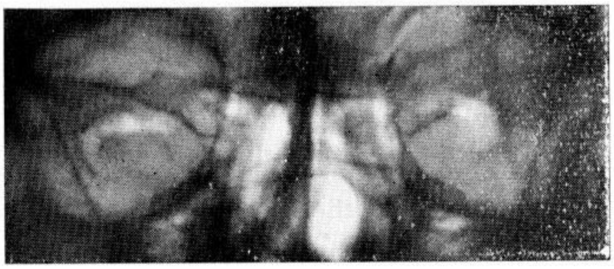


4 d

Fig. 4. - *a, b, c and d. — Fractioned encephalography in a case of left multiform temporal glioblastoma. The contrast does not penetrate the supratentorial part of the ventricular system, but only the fourth ventricle is visualized, and the inferior portion of the aqueduct is displaced to the right (a). After the administration of urea the contrast penetrates easily the lateral ventricles and the third ventricle, showing the existance of a tumor in the left hemisphere (b) from where the study of the temporal horns proves its infiltrating nature (c and d). Actually the left temporal horn is medially displaced, lifted and its contour appears irregular.*

We are fully aware of the fact that non-neuroradiologists may find all these small and big signs rather intricate. However the difficulty of the examination does not deprive it of its value; it just emphasizes that encephalography must be carried out by a specialist.

At any rate, let us summarize schematically the main signs of the most common types of tumors of the posterior fossa:

Cerebellar hemisphere tumors and meningiomas of the tentorium and lateral sinus. — Fourth ventricle displaced anteriorly and to the opposite side: aqueduct diaplaced anteriorly, to the opposite side an "kinked"; posterior portion of the third ventricle lifted; pontine cistern displaced anteriorly with accentuation of its posterior concavity; filling defect of the extracranial portion of the cisterna magna.

Tumors of the cerebello-pontine angle. — Aqueduct and fourth ventricle lifted and displaced backward and to the opposite side. Cistern of the homolateral cerebello-pontine angle lifted.

Meningiomas of the clivus. — Upward and posterior displacement of the aqueduct and of the fourth ventricle; pontine cistern displaced posteriorly.

Pontine glioma. — Aqueduct and fourth ventricle displaced upward and posteriorly; pontine cistern normal or slightly distorted and pushed anteriorly.

Hemispheral Tumors

It would certainly defeat the purpose of this paper, should we begin any discussion on the pneumoencephalographic diagnosis of the brain tumors, which is mainly based upon the outlining of the ventricular system with the exception of the parasagittal tumors. We shall limit to mention only the most recent progress in the diagnostic field. The urea technique has made it possible for us to eliminate in almost all the cases the inconvenience of an insufficient filling or of a non-filling of the ventricular system (fig. 5), with the exception of intraventricular tumors, the lack of filling is always due to edema with a twofold mechanism: a direct one, by flattening the lateral wall of the ventricle itself and an indirect one by causing a rather large temporal herniation which in turn squeezes the brain stem against the free margin of the tentorium with consequent stenosis of the aqueduct. In both instances the sumministration of urea will be greatly useful by decreasing the edema and thus allowing the passage of the contrast medium into those regions of the ventricular system not priorly visualized. In several cases it might be possible to localize even with a fair accuracy a brain tumor by visualizing the subarachnoid space alone. However it would be extremely difficult to make a diagnosis which would not be open to some sharp criticism.

The localization of a hemispheral tumor can be achieved in the great majority of the cases by means of carotid arteriography even though no newly-formed pathological vessels may be present. However it is not so easy to establish how deeply located the lesion is, which is, without fail, a diagnostic element of paramount importance in the field of modern neuroradiology which feels conceited enough to suggest to the surgeon the eventual criteria of operability. In three circumstances pneumoencephalography demonstrates in our opinion, its superiority over arteriography: 1) Tumors infiltrating and invading the ventricles. 2) Parasagittal tumors. 3) Temporal tumors.

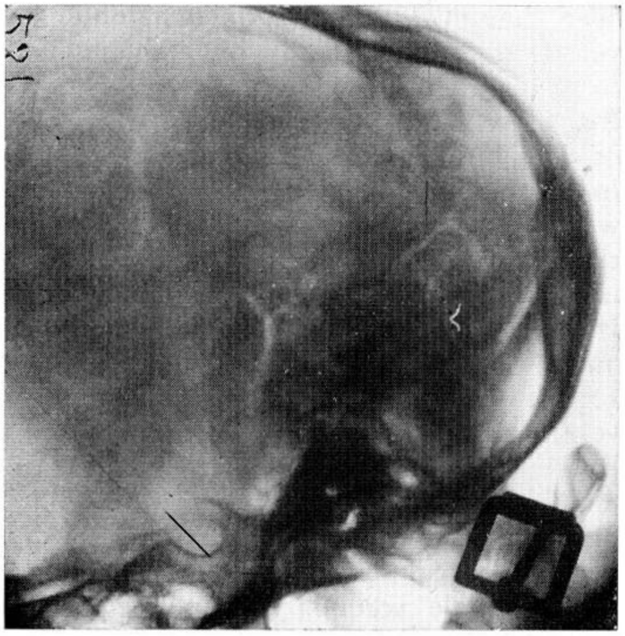
We shall only limit to emphasize the criterion in order to differentiate an intraventricular tumor from a tumor invading the ventricle secondarily. In the former case the ventricle is dilated and shows a filling defect but it is not displaced or if so, very slightly. In the latter one, the ventricle is markedly displaced and its walls are indented.

In temporal tumors the three main elements of an arteriographic localization are: the calvarium; the Sylvian group and the anterior cerebral artery, whereas the elements of an encephalographic localization are four: calvarium, Sylvian sulcus, temporal horn and septum pellucidum. It is indeed the temporal horn that makes it possible to locate the lesion laterally or medially to the ventricle thus defining its relationship with the basal ganglia.

In parasagittal tumors the outlining of the cistern of the corpus callosum allows a substantial differentiation between a meningioma of the falx, in which surgery is mandatory, and an intracerebral tumor infiltrating the corpus callosum, making surgery not only unnecessary but also not advisable.

Suprasellar Tumors

There is no doubt that the superiority of fractional air study above all of the other means of investigation has been widely accepted in this type of pathology, for only this technique can point out with certainty whether a tumor is intra or extracerebrally located and thus solving the diagnostic



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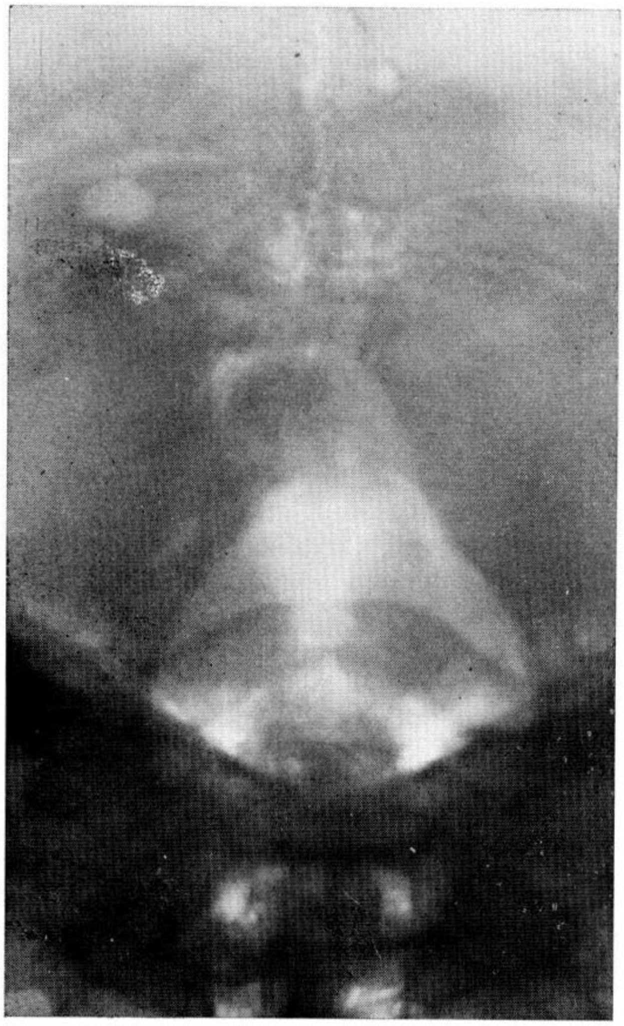

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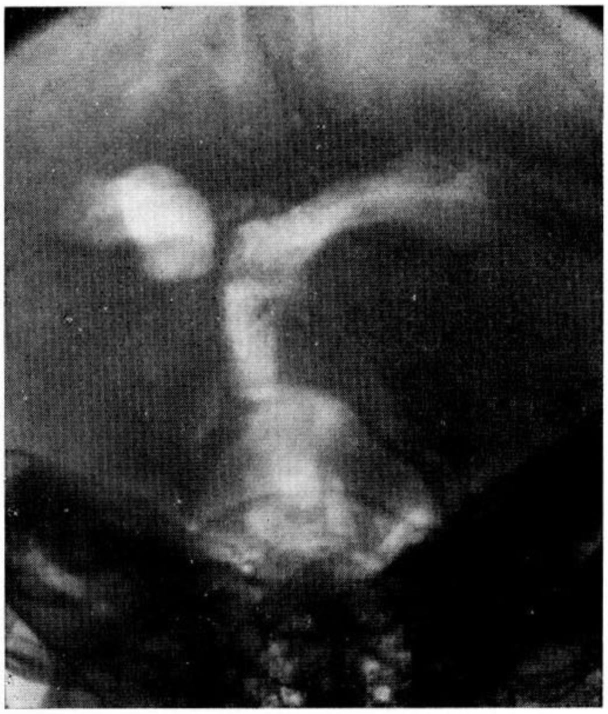

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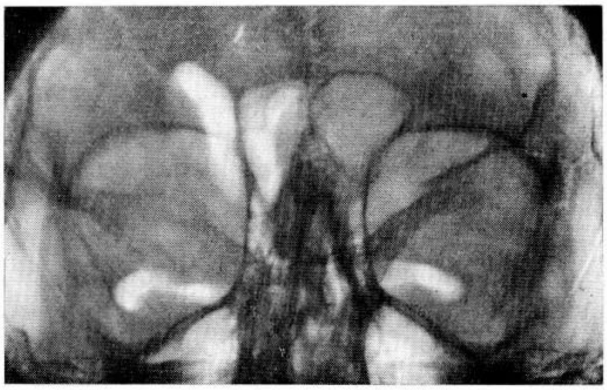


5 d

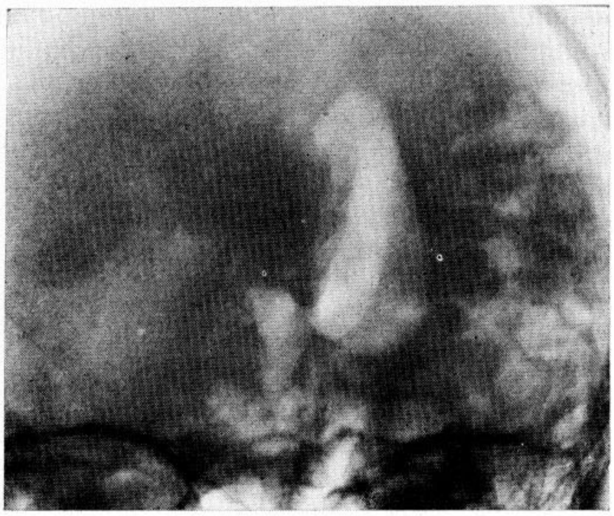
Fig. 5. - *a, b,* c *and* d. — *Fractioned encephalography in a case of left fronto-parietal subdural hematoma. The contrast does not penetrate the supratentorial part of the ventricular system; the brain stem appears displaced downwards and to the right (a and b). With the administration of urea the contrast passes easily to the supratentorial part of the ventricular system (c), which appears displaced in block to the right keeping, however, a normal-appearing morphology (d).*

problem and giving a determining contribution towards the type of therapy: Surgical treatment, stereotactic surgery, Rcentgetherapy, etc. As far as the mere localization of these tumors is concerned, encephalography may even be valueless, for the intrasellar, and suprasellar tumors are usually easily diagnosed on the basis of the anamnesis, of the neurological examination and of the x-ray examination of the skull.

The encephalographic diagnosis is based upon a comparative study between the outlining of the ventricular system and that of the suprasellar cisterns. The typical feature of the latter ones is as follows: in the intracerebral tumors the cisterns are pushed downward and compressed; whereas in the extracerebral ones they are lifted and they often outline the contour of the tumor. However, their visualization is not so easy as it might seem; in very large space-occupying lesions the cisterns may be so poorly filled to render their interpretation rather difficult. In these cases one must pay attention to the ventricular contours: in the extracerebral tumors, even if the third ventricle is markedly distorted and displaced upwards, the outlining of its antero-inferior portion can always be individualized and the chiasmatic and the hypophisary recesses are usually farther apart from each other. In the cases of infiltrating gliomas the ventricular outlining is always completely distorted. A very accurate technique is indispensable. The cisterns must be studied with the patient both in the sitting and in the supine positions. Tomography may undoubtedly bring forth some further information, however the most useful information may be gained by taking some control films few hours after the air study. The reabsorption of the air from the subarachnoid spaces occurs more rapidly than in the ventricles; for this reason the delayed controls may show more clearly some portions of the ventricular system which were formerly ill defined due to the superimposition of the subarachnoid air. It is sometimes possible to observe surprising changes in the whole picture without fully understanding its mechanism of action. We would like to mention as an example of what was just said, the case of a patient whose air study showed an amputated frontal horn, suggesting the presence of an infiltrating intraventricular tumor; which at an eight hour control appeared to be perfectly well visualized and displaced upwards. The final diagnosis, controlled there after surgery, was that of a craniopharyngioma. We have also been able to demonstrate with delayed controls the presence of poroencephalic cysts which were not visible at the time of the examination. Brain tumors arising and/or involving the midline structures.

All the tumors taking their origin from the anterior portion of the septum pellucidum as far back as the pineal region and the cerebral peduncles, together with the thalamic tumors, will be grouped and discussed in this chapter (the tumors of the pons and of the fourth ventricle belong to the posterior fossa group even though they occur within midline structures).

As far as the gliomas of the corpus callosum are concerned, we have already mentioned the usefulness of studying the cistern of the corpus callosum in order to differentiate them, if necessary, from the meningiomas of the falx. In the very large thalamic tumors a typical sign will be present: the upward displacement of the floor of the lateral ventricles giving rise to a downward concavity. The pineal region tumors do not usually entertain any difficulty in diagnosing them, provided the ventricular system be visualized. In these cases, as well as the tumors of the foramen of Monro, ventriculography is often mandatory. The outlining of the posterior portion of the third ventricle and of the superior portion of the aqueduct is typical. In pinealomas there is a characteristic distortion of the posterior portion of the third ventricle which appears to be amputated and concave downwards, whereas in the gliomas of the quadrigeminal plate there does exist some "straightening" of the inferior portion of the posterior margin of the third ventricle and of the upper portion of the aqueduct, which is often stenotic. The type and the degree of the stenosis are to be considered of pa-



6 a

6 b

Fig. 6. - *a and b. — Fractioned encephalography in a case of spontaneous acute intraventricular hematoma.*

ramount importance in order to differentiate a tumor from an inflammatory type of occlusion. However, it is our opinion that greater emphasis should be placed upon the outlining of the cisterns of the brain stem and more so of the cistern of the vein of Galen, which is ill visualized and distorted in the case of a tumor, whereas it will appear dilated secondary to atrophy of the brain stem in those stenosis of inflammatory origin.

In the tumors of the cerebral peduncles encephalography makes it possible a living anatomical study of the region, for the brain stem is surrounded by cisterns and especially the cisterna ambiens.

A more detailed diagnostic discussion on these different types of tumors goes far beyond the aim of this paper, however there is no doubt that a diagnostic progress has been achieved since our monography on encephalography, in which this chapter on tumors arising from the midline structures is completely wanting. We would like to state further that it is rare and perhaps impossible to find tumors strictly located withing the upper brain stem; they are usually gliomas extensively infiltrating the mesencephalon and/or the diencephalon. In the so-called pinealomas it is often possible to see, besides the filling defect of the posterior portion of the third ventricle, signs of invasion within one of its lateral walls and consequently of the thalamus. Almost all the gliomas of the quadrigeminal plate encountered by us, were found to be creeping anteriorly and superiorly towards the pulvinar and the splenium of the corpus callosum, whereas their downward extension with invasion of the peduncles, could be ascertained by observing the distortion of the cisterna ambiens.

This diagnostic progress, partly due to a technical progress, has so limited surgical intervention in this group of tumors to almost eliminate. One might be tempted to feel sorry for it if new horizons did not open to a more proper treatment of these lesions: isotope implantation through stereotactic surgery. These new procedures necessitate a meticulous precision in localizing the tumor and in outlining the contours, in order to avoid bringing any untoward lesion to surrounding normal structures. Encephalography has undoubtedly given a great contribution to the development of these new techniques.

Encephalography in head injuries and cerebro-vascular accidents

We have been able to demonstrate with encephalography the presence of intraventricular hematomas (fig. 6) in those cases, in which bilateral carotid arteriography had completely failed to do so. In the head injury cases a negative air study together with a negative arteriography will certainly rule out the presence of posterior fossa hematomas and thus it will eliminate any possible surgical exploration which might further aggravate the patient's condition.

This last statement as to the indications of encephalography might well be, in our opinion, an appropriate conclusion to this paper, in which we have tried our best to place emphasis on the most recent technical and diagnostic advancements in the field of pneumoencephalography in regard to the space-occupying lesions of the brain.

SUMMARY

This paper is a schematic outline of the main aspects of fractioned encephalography in cerebral tumors, in the light of the latest technical developments (administration of urea, delayed control) and of interpretation of radiograms.

The question of pneumoencephalographic diagnosis of posterior fossa tumors is critically discussed, with particular regard to the diagnosis of lateral tumors in the brain hemispheres and the localization of tumors in the fourth ventricle.

Fractioned encephalography is the technique to be chosen in cases of extracerebral tumors in the cranial basis, as it allows diferential diagnosis with intracerebral tumors in the diencephalon and mesencephalon.

In supratentorial tumors, the perfusion of urea during encephalography has practically suppressed the inconveniences of insufficient filling of the ventricles caused by cerebral oedema. This technique has undoubtedly constituted a fundamental progress in diagnosis in the field of cerebral hemisphere tumors. Radiographic control effected furthermore some hours (generally form 6 to 8) after the examination, is also useful because it allows an improved visualization of the ventricular images which appeared concealed, in the subarachnoid space. In the latter case the air is more rapidly reabsorbed than in the ventricular system.

The paper concludes, reminding the usefulness of pneumoencephalography in acute vascular accidents, traumatic or not, where this technique proved to be a fundamental aid to carotid arteriography.

RESUMEN

Este trabajo reúne los aspectos fundamentales relacionados con el empleo de la encefalografía fraccionada en tumores cerebrales, de acuerdo a recientes conquistas en su técnica (suministro de urea y controles radiográficos de 6 a 8 horas después del examen) y en su diagnóstico.

El problema del diagnóstico neumoencefalográfico de los tumores de la fosa posterior es considerado particularmente con miras a la posibilidad de establecer el lado involucrado y la localización intraventricular del tumor dentro del cuarto ventrículo.

La encefalografía fraccionada es la técnica más indicada en los tumores extracerebrales de la base del cráneo, ya que permite el dignóstico diferencial con respecto a tumores intracerebrales diencefálicos y mesencefálicos.

En los procesos expansivos supratentotiales, la técnica del suministro de urea ha eliminado prácticamente el efecto negativo de la falta parcial o total de relleno de los ventrículos laterales debida al edema cerebral.

Esa técnica ha permitido un progreso diagnóstico considerable en el dominio de los tumores cerebrales hemisféricos. Un control radiográfico realizado pocas horas (generalmente de 6 a 8 horas) después de

la encefalografía resulta igualmente útil. De hecho con esta técnica es posible obtener una mejor visualización de los detalles ventriculares, que eran difíciles de diferenciar de la imagen del espacio subaracnoideo, porque el aire es más rápidamente reabsorbido que en los ventrículos.

Por último el autor señala el valor de la encefalografía fraccionada en los accidentes vasculares agudos —traumáticos o no— en que esta técnica puede significar una ayuda útil a la exploración angiográfica.

RÉSUMÉ

Ce travail est un aperçu des aspects essentiels de l'encéphalographie fractionnée dans les tumeurs cérébrales à la lumière des acquisitions les plus récentes dans le domaine de la téchnique (administration d'urée, contrôles à distance) et de l'interprétation des clichés.

On revoit de façon critique le problème de diagnostic pneumoencéphalographique des tumeurs de la fosse postérieure, en insistant sur les progrès les plus récents: le diagnostic de côtè des tumeurs des hémisphères cérébelleux et celui des tumeurs dans le quatrième ventricule.

L'encéphalographie fractionnée est la méthode l'éléction dans les tumeurs extracérébrales de la base du crâne qu'elle permet de différencier de celles intracérébrales des régions diencéphalique et mésencéphalique.

Dans les tumeurs supratentorielles l'association à l'encéphalographie de l'administration d'urée supprime pratiquement les inconvénients du remplissage insuffisant des ventricules à cause de l'oedème. Ceci constitue un progrés important du diagnostic des tumeurs hémisphériques. De même les contrôles radiographiques pratiqués quelques heures (en général de 6 à 8) après l'encéphalographie sont utiles, surtout pour mieux interpréter des immages ventriculaires masqués par les espaces sous-arachnoidiens, car dans ceux-ci l'air se résorbe plus rapidement que dans les ventricules.

On rappelle enfin l'utilité de l'encéphalographie dans les syndromes aigus d'hémorragie cérébrale (traumatique ou non), où elle peut se révéler un complément de l'artériographie d'une importance insoupçonnée.

ZUSAMMENFASSUNG

Diese Arbeit ist eine schematische Darstellung der wichtigsten Aspekte der fraktionierten Enzephalographie bei Hirntumoren unter Beruecksichtigung der neuesten technischen Fortschritte (Verabreichung von Urea, die radiologische Kontrolle nach 6 - 8 Stunden, und der Deutung der Radiogramme).

Das Problem der pneumoenzephalographischen Diagnose der Tumoren in der Fossa posterior wird kritisch besprochen unter besonderer Beruecksichtigung der moeglichen Lokalisierung der Seite eines Tumors der zerebellaeren Hemisphaere und der intraventrikularen Lokalisierung eines Tumors des vierten Ventrikels.

Die fraktionierte Enzephalographie ist die Technik der Wahl bei extrazerebralen Basaltumoren, da sie die Differenzialdignose gegenueber intrazerebralen Tumoren des Dienzephalons und Mesencephalons erlaubt. Bei den supratentorialen Tumoren hat die Perfusion von Urea waehrend der Enzephalographie praktisch die Schwierigkeiten der durch Hirnoedem verursachten ungenuegenden Fuellung oder Nichtfuellung der Ventrikel beseitigt. Diese Technik ist ohne Zweifel ein grundlegender Fortschritt bei der Diagnose der Hemisphaerentumoren. Die radiologische Kontrolle die ausserdem einige Stunden (6-8 Stunden) nach der Untersuchung ausgefuehrt wird,

ist ebenfalls nuetzlich weil sie eine verbesserte Sicht der véntrikulaeren Details erlaubt, welche nur mit Schwierigkeit von den Gebilden im subarachnoidalen Raum differenziert kerden konnten. In diesem ist die Luft schneller reabsorbiert als im ventrikulaeren System.

- Die Arbeit schliesst, indem sie an die Nuetzlichkeit der fraktionierten Enzephalographie bei akuten Gefaesstoerungen traumatischen oder nicht traumatischen Ursprunges, wobei diese Technik sich von grundlegendem Vorteil bei der Angiographie erwies.

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The Place of Electro-Encephalography in the Diagnosis of Cerebral Tumors

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It is 35 years ago since Hans Berger published his first paper "Ueber das Elektrenkephalogram des Menschen" and 28 years since Grey Walter showed that it is possible to locate a cerebral tumor with the aid of this method.

Electroencephalography is practised throughout the world, particularly in cases suspected of having a cerebral tumor. Still the opinions concerning the value of this method for the diagnosis of cerebral tumors vary greatly, particularly amongst neurosurgeons who are in charge of the patients and who have the responsibility for their treatment. Other methods, such as for instance pneumoencephalography and cerebral angiography have been perfected, so that they are less nocuous and provide better information than 10 or 15 years ago. And new methods such as the investigation of the brain with ultrasound (echo-encephalography) or with radio isotopes (gamma-encephalography and measurement of the cerebral circulation) have been developed and are applied to a rapidly increasing degree.

For these reasons it may be useful to reconsider the place of electro-encephalography in the framework of the diagnosis of cerebral tumors.

We cannot, in this short review, give a survey of the EEG abnormalities caused by a cerebral tumor. In recent years a number of publications has been devoted to the various aspects of this subject (Bágchi [1]; van der Drift [5, 6, 7]; Hess [11]; Bechterewa [2]; Magnus [13], Storm van Leeuwen and Cobb).

There are however a number of aspects which are by no means new, still do not always receive the attention which they deserve.

1. The cerebral tumor is electrically inactive. The EEG can therefore not give direct information on the site and extent of a cerebral tumor. What is reflected in the EEG is the change to which the tumor gives rise in the grey matter of the brain. In this, as in many other respects, the EEG-findings resemble those of the neurological examination: a cerebral tumor can only be detected directly for instance by the presence of an intumescence of the skull. In the large majority of cases the clinical tumor signs are due to increased intracranial pressure and/or to a disturbance of function of certain brain areas as a consequence of the presence of the neoplasm. It is fortunate that the EEG gives an indication of a quite different type of disturbance of cerebral function: in this way it can give valuable complementary information to the neurological investigations.

2. Though we know only relatively little about the pathophysiology of the EEG, i.e. about the factors which are responsible for the EEG changes, it is in most cases of hemisphere neoplasms possible to make a correct localization. The most important localizing sign is the presence of

a silent area. Often there is no complete electrical silence, even in the region over a tumor, but rather a depression of faster background activities of the alpha, beta- and theta- range with in the same region irregular or polymorphic delta activity *.

Usually the slowest and the most irregular delta activity is nearest to the lesion. Intermittent and/or rhythmic delta activity has much less localizing value and this is usually even more true for theta activity. Of course in the early stages of a neoplasm local theta activity over the tumor may be the only EEG abnormality. We can readily understand this when we realize that the cortex overlying a tumor in the early stage may be affected in a similar way as the cortex more at a distance at a later stage.

It is well known that the EEG gives best results in cases of space occupying lesions in the cerebral hemispheres. Tumors of the brainstem generally give less specific abnormalities; they are to a certain extent similar to those which are seen at a distance from the lesion in hemisphere tumors.

Subtentorial lesions by themselves usually do not give rise to abnormalities in the EEG. They do so when they interfere with the circulation in supratentorial structures either as a consequence of increased intracranial pressure or by direct obstruction of cerebral vessels. In children this tends to give rise to slow activity in posterior regions, in adults the slow activity is often most marked over the frontal lobes.

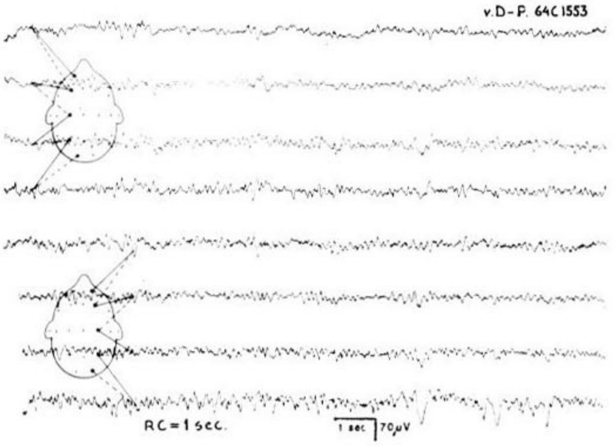
* Often this delta activity has a considerable voltage so that the amplification must be reduced which makes it difficult to evaluate the faster background activity. In such cases it is necessary to reduce the time constant to about 0.02 or 0.03 sec. and to increase the gain in order to be able to judge asymmetries of this activity. Normally the EEG must be recorded with a time constant of at least 0.3 sec. and preferably with a time constant of 0.5 or 1 sec. If there is very slow delta activity this becomes often clearer on recording with a paper speed of 0.5 to 1.5 sec. These technicalities may seem irrelevant but in fact it is our experience that too often they are neglected which may lead to erroneous interpretations. It is always necessary to look especially for the depression of the background activity because it is a much less prominent feature of the EEG than the delta activity.

3. A very important factor in determining the type and degree of abnormality of the EEG is the speed with which a space occupying lesion develops. If a lesion as for instance a meningioma of the lesser wing of the sphenoid grows very slowly, it may reach a considerable size without giving rise to any abnormalities in the EEG. If there are abnormalities they tend first to be more of an "irritative" nature, i.e. they consist of paroxysms of sharp waves, complexes of sharp and slow waves or sometimes spikes. Then there may be a change in the background activity, either an increase or decrease of the amplitude or a change in the frequency or the regularity. A much smaller lesion developing rapidly usually causes much more marked changes in the EEG and this is even more true for acute space occupying lesions, such as haemorrhages and also for rapidly growing cysts. It is apparently very important to what degree the brain is able to adapt to the growing lesions. For this reason we can usually distinguish between a stage of compensation and a decompensated stage (van der Drift [5, 6, 7] and Magnus [13]).

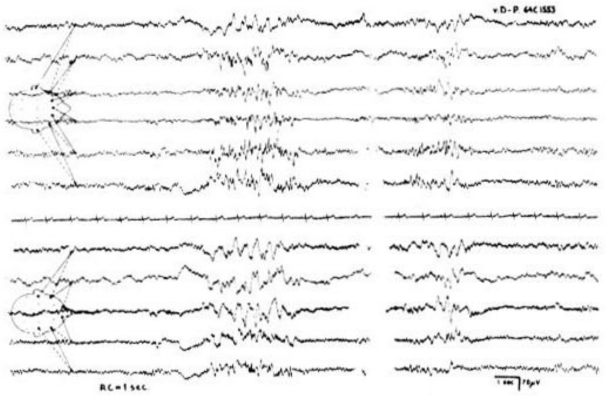
Here again there is a parallel with the clinical picture: slowly growing tumors may reach a considerable size before giving rise to clinical symptoms and then the first sign may be the development of epileptic phenomena; rapidly growing lesions usually cause symptoms in an early stage.

4. One of the most important factors in determining EEG abnormalities both in the region of the tumor and at a distance is a disturbance of the circulation. On studying the cerebral circulation with the aid of radioactive isotopes in cases with cerebral tumor, there appeared to be a certain correlation between the slowing of the circulation and the degree of the abnormalities of the EEG (van der Drift [5, 6, 7], Magnus [13] and van den Berg).

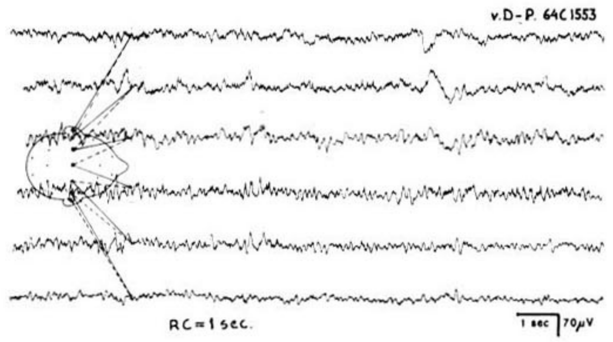
Particularly in old persons with a space occupying lesion the disturbances of the circulation may dominate both the clinical picture and the EEG. In such cases the history may be typical for recurrent cerebral ischaemic attacks and the EEG may also show disturbances suggestive of a vascular



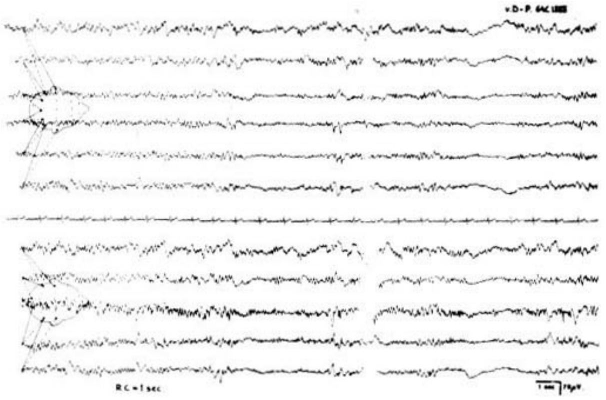
A. — Alpha-and beta frequencies are of lower voltage on the left side. There is more slow activity of theta- and delta- frequencies in the right occipital region.



C. — Burst of bilaterally synchronous 11-12 c/s activity mixed with 2–2½ c/s waves. The faster activity in less, the slow activity more marked on the left side.



B. — Less mu rhythm, more theta activity on the left side. Delta waves in the left temporal region.



D. — Less alpha activity on the left side, more theta– and delta activity, particularly in the temporal region.

Fig. 1. — *Mrs. v.D.-P. E.E.G.*

lesion. Only further investigations (echo-encephalography and, if this is positive cerebral angiography) will reveal that this syndrome is secondary to a cerebral tumor or another type of a space occupying lesion such as a subdural haematoma. It is always necessary to think of this possibility in cases suspected of having a cerebral ischaemic lesion.

5. This is one of the conditions in which *echo-encephalography* with ultrasound has proved particularly valuable.

With this method the reflections of ultrasound pulses against transition surfaces of the brain such as the wall of a ventricle, the falx or the inner table of the skull, are used to locate these surfaces within the skull. Median structures such as the third ventricle and the falx have proved to give particularly clear and constant ultrasound echo's. With some experience displacement of these structures can be detected with a reliability of better than 90% (de Vlieger and Ridder [19]; Lithander [12]; Ford and Ambrose [10]; Schiefer et al. [17]).

The relatively elementary information, whether or not there is a shift of midline structures often proves to be very important for the decision whether there is a space occupying lesion, i.e. whether further diagnostic measures should be taken in view of neurosurgical intervention. In general this method is particularly useful in combination with the EEG as the 2 methods

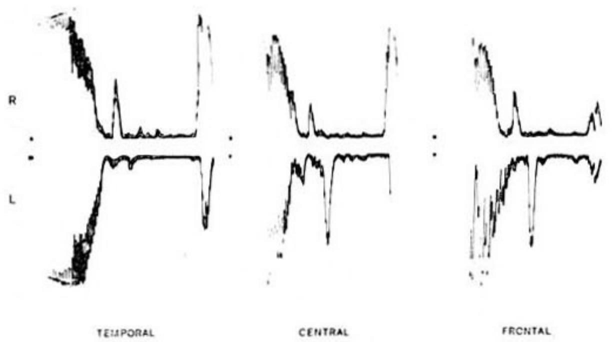


Fig. 2. — *Mrs. v.D.-P. Echo-encephalogram.*

Shift of the deflections of the midline echo with the transmitter-receiver in the temporal, central and frontal regions. The pictures obtained with the probe on the left side are presented upside down in order to facilitate comparison. When transmitting from the right side the midline deflection is more to the left in the diagram indicating a shorter distance from the midline to the probe, when transmitting from the left side the midline deflection is more to the right, indicating a longer distance midline to probe.

are complementary to each other. The EEG often provides a good lateralization and location of a lesion and gives valuable information as to the general condition of the brain. But it can give only indirect and uncertain indication as to whether a lesion is space occupying. The echo-encephalogram on the other hand gives practically no information concerning the lesion itself but it tells whether there is a space occupying or retractive process on the side of the lesion demonstrated by the EEG.

As both these methods are harmless and can easily be performed and repeated in outpatients they enable one in conjunction with the neurological examination to arrive at a satisfactory preliminary diagnosis and at a better selection of patients for admission to the hospital in the large majority of the cases.

6. Another method, *gamma encephalography* uses the fact that certain substances after intravenous injection are stored with higher concentration in certain brain tumors than in the surrounding brain tissue. When these substances are labelled with radioactive isotopes the radiation over the various brain areas can be measured and the activity over symmetric areas can be compared. Various substances are used e.g. radioactive iodinated human serum albumine (RISA), chlormerodrin tagged with mercury 197 or mercury 203 etc. (Planiol [16]; Dugger and Pepper [8]; Sweet et al. [18]; Feindel et al. [9]).

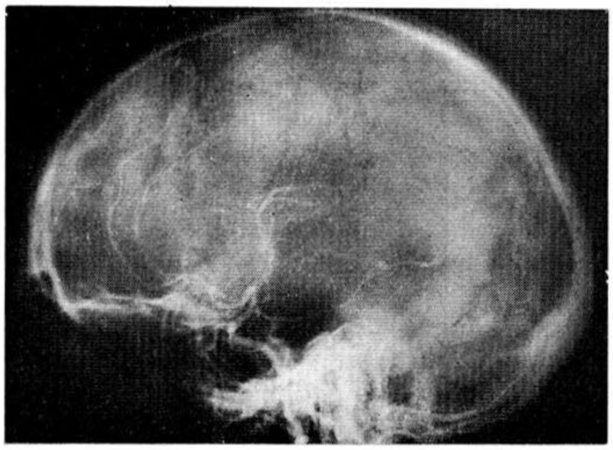
A number of measurements is made over the skull either with manual positioning of the scintillation probe or with an automatic scanning device. In our hospital RISA encephalography is used and measurements are made 1, 24 and 48 hours after the injection, so that the way in which the isotope is stored in and washed out from the different brain areas can be followed and compared. This method gives not only an indication of the location but also of the type of the lesion. As compared with EEG it has the advantage of giving a direct indication of the actual site of the tumor. It also enables one to detect the presence of several tumors such as metastases. If necessary it can be applied in outpatients.

A drawback of the method is that because of the radioactivity it is not completely harmless and should not be applied indiscriminately particularly in young subjects. When radioactive iodine is used the patient must be prepared with Lugol's solution in order to protect the thyroid gland. It is also a complicated and time consuming method. However, with selected patients, it gives very valuable indications as to the presence, location and type of a cerebral tumor.

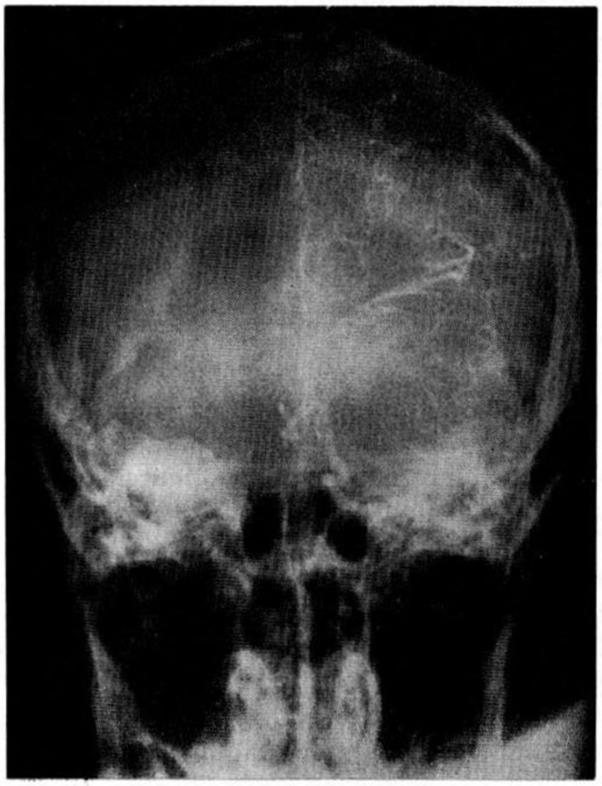
Of course the combination of these various methods, which can be applied to outpatients, gives a much higher degree of certainty concerning the type and location of a lesion. At least as important however is that in many cases they can help to exclude with a higher degree of reliability the presence of a space occupying lesion.

The following case-histories may serve to illustrate some of the points discussed above.

Mrs. v. D.-P., 37 years of age was referred to a neurologist because of 2 attacks



A. — Lateral view. Note marked upward displacement of the middle cerebral artery and forward shift of the anterior cerebral artery. Downward displacement of the posterior cerebral artery.



B. — A-P view. Large displacement of the middle and posterior cerebral arteries, only little displacement of the anterior cerebral artery over the midline.

Fig. 3. — *Mrs. v.D.-P. Left carotid angiogram.*

of unconsciousness, which had occurred with an interval of 3 months, both times after an emotional upset. They were associated with jerks and turning of the head to the right and a tonic extensor spasm lasting for half an hour. The period of unconsciousness lasted for 5 hours.

After a head injury at the age of 20 she had had headaches which had gradually diminished during the last year. Likewise at the age of 20 she had had an anxiety state. Since that time she had occasional short spells of dizziness without a disturbance of consciousness.

On examination the patient was alert, tense and nervous. She appeared to be physically fit and no neurological abnormalities were found. Straight x-rays of the skull revealed no abnormalities.

The EEG (fig. 1) however revealed as most important abnormalities the presence of focal irregular delta activity in the left anterior temporal region and paroxysms of irregular bilaterally synchronous fast and slow activity, mixed with spikes. The fast components were less marked in the left frontal region, on that side however there was more intermittent rhythmic delta activity. The findings were considered to indicate that there was a lesion in the left anterior temporal or fronto-temporal region and of an irritative brain stem disturbance.

The echo-encephalogram (fig. 2) showed that there was a marked displacement of midline structures to the right side, the temporal, central and frontal echo's being displaced about 5%, corresponding with a shift of the midline of about 1 cm beyond the median plane. Because of these findings the patient was admitted to the hospital, where the above findings were confirmed. The left carotid angiogram (fig. 3) showed a very marked displacement of the anterior and middle cerebral arteries and pathological vessels over the lesser wing of the sphenoid, indicating the presence of a large expanding lesion in this area. With gamma encephalography (fig. 4) there was some hyperactivity in the left anterior temporal region, increased after 24 hours.

On these findings a probable diagnosis of meningioma of the lesser wing of the sphenoid was made. The patient refused operation. She was discharged with the advice to remain under close neurological supervision.

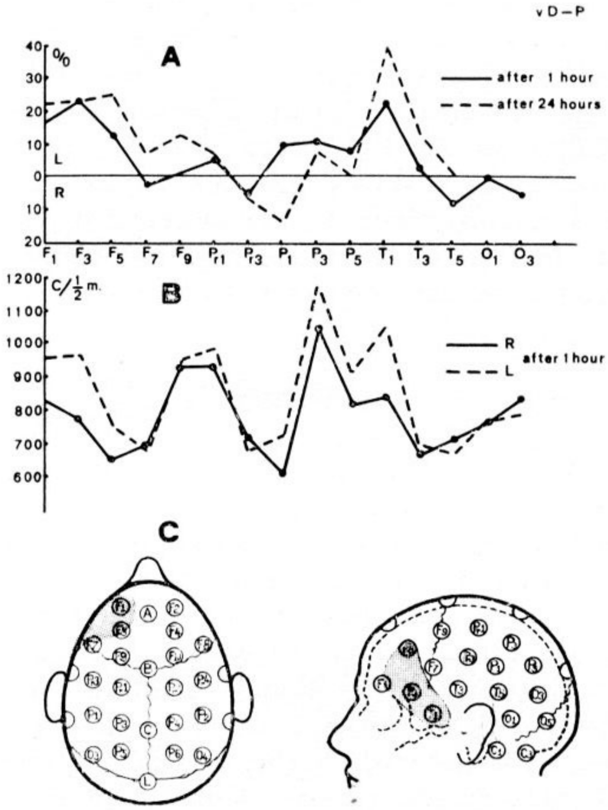


Fig. 4. — *Mrs. v.D.-P. Gamma encephalogram.*

A. — Percentual difference between the counts from the left and right side after 1 and 24 hours respectively. Abscissa: locations of the collimator as indicate in C.

B. — Values of the radioactivity in counts per 30 sec. measures after 1 hour on the right and left side respectively.

C. — Diagram indicating the area of hyperactivity.

Comment

There was a striking discongruence between the paucity of clinical signs on one hand and the clear abnormalities in the EEG and the echo on the other hand, suggesting that this was a slowly growing lesion having led to a very strong displacement without appreciable loss of function. In other words, notwithstanding its size the lesion was still in the compensated stage. This also explains why the patient refused operation. In view of future developments it is still very important to be as well as possible informed about this lesion.

———

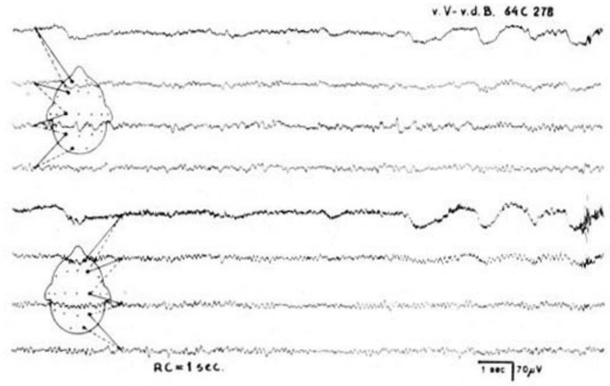
Mrs. v. V.-v.d.B., 37 years of age complained since 9 months of seizures of the following type: The face drew to the left, the tongue became stiff and she had difficulty in speaking; she had a bad taste and then a stiff feeling in the right hand.

Consciousness was not altered during these spells. Later she also had a tremor in the right arm and leg at the end of the seizure. These attacks were associated with a right frontal headache: later this headache became more continuous and generalized. The patient was predominantly lefthanded. On examination the right pupil was larger than the left. Other positive signs were: a slight papilloedema; a mild weakness of the left arm; disturbed joint sensation in the left hand; increased tendon reflexes and pathological reflexes in the left leg. Clinically there were therefore signs pointing to a lesion on the right as well as on the left side.

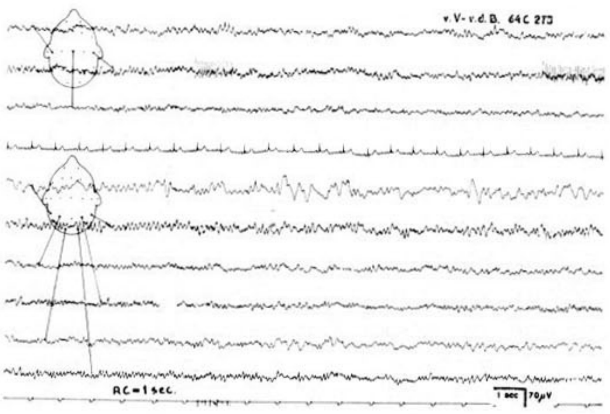
In the EEG (fig. 5) the alpha rhythm, the beta rhythm and the mu rhythm had a lower amplitude on the left side. The response to photic stimulation was more marked on the left side for low frequencies and less for high frequencies. In the left temporo-occipital region there were runs of 2-3 c/s delta waves, which were sometimes mixed with sharp waves. There was occasionally some independent paroxysmal activity in the right temporal region. These findings were considered to indicate the presence of a moderately active lesion in the left hemisphere, probably predominant in the left parieto-temporal region.

The echo-encephalogram showed a considerable displacement (approximately 1½ cm) to the right.

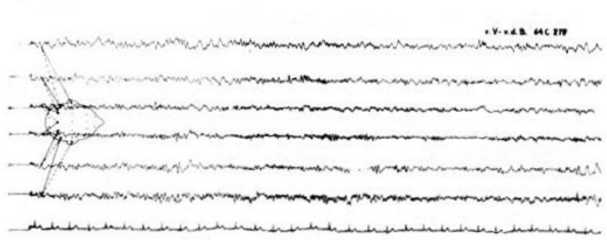
Therefore there was now clear evidence for the presence of a space occupying lesion on the left side probably in the parieto-temporal region. The left carotid angiogram gave evidence for the presence of a large centro-parietal tumor, probably a meningioma (fig. 6). The circulation time was somewhat increased on the left side: CTD ½: 3½ sec. (normal value: 2½-3 sec). At operation a large centro-parieto-temporal meningioma was removed. The patient made a good recovery with only a residual right hemianopia.



A. — The alpha activity is less marked on the left side. Delta– and theta–activity is seen in the left parieto–occipital region.



B. — Recording to the average reference. Less alpha–activity on the left side. Theta– and delta– activity, maximal in the left posterior temporal region.



C. — Similar findings in a bipolar recording.

Fig. 5. — *Mrs. v.V.–v.d. B.*

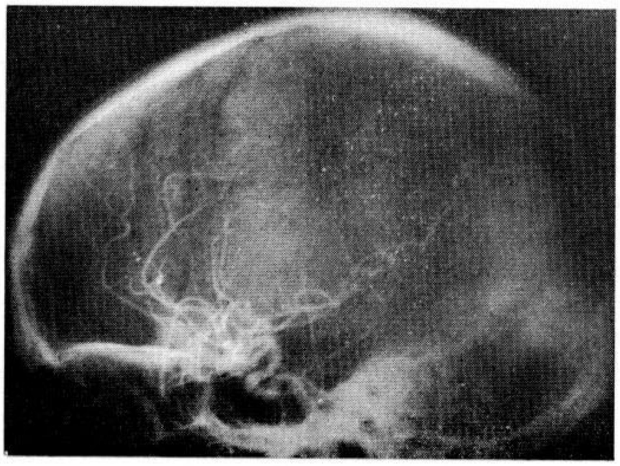
Comment

In this case it was not possible to make a location on the clinical data alone. The EEG and echo encephalogram however provided a lateralization and location. The marked displacement seen on the echo, together with relatively moderate abnormalities in the EEG were in favor of the presence of a slowly growing tumor such as a meningioma. As the angiogram also was in favor of a meningioma, no gamma-encephalogram was done in this case.

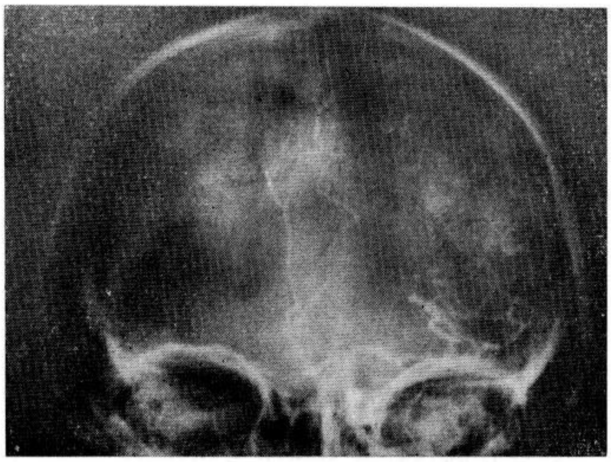
DISCUSSION

With the advent of new diagnostic methods and the improvement of older techniques, the EEG retains its value for the diagnosis of cerebral tumors. Modern diagnosis does not rest on one method but on the integrated information of a battery of diagnostic procedures, beginning with the taking of the case history and sometimes ending with highly specialized and complicated techniques. As several of these methods, like the EEG, are harmless and can be applied on outpatients, it is often possible to arrive at a fairly accurate diagnosis before admission of the patient to the hospital. And not less important — with these methods the selection of patients for admission to the hospital is improved, early admission of patients requiring treatment being promoted and unnecessary admissions being reduced. The complexity of the newer diagnostic methods should however not lead to a technical approach to the diagnostic problem. Modern electro-encephalography for instance requires highly specialized equipment and furnishes very complex data. Still it is in essence a "clinical" method, reflecting the variable condition of the brain in its own particular way.

Just because the various methods of examination such as the taking of the case history, the neurological examination, the EEG, the echo-encephalography, isotope studies, the various radiological methods and the laboratory investigations, each provides information on different aspects of the condition of the brain, does the combination of the results give a much higher



A. — Lateral view. Upward and forward displacement of the anterior cerebral artery, downward displacement of the middle cerebral artery.



B. — A-P View. Marked shift of the anterior cerebral artery over the midline. Vessels surrounding the tumor are seen in the parieto-temporal region.

Fig. 6. — *Mrs. v.V.-v.d.B. Left carotid angiogram.*

degree of reliability than each method alone.

Electro-encephalography has in common with other methods that it sometimes by itself can give a statement concerning type and location of a lesion and at other times gives no or only limited information which derives its value only from combination with the results of other methods.

As those who are responsible for the treatment of the patient often have only a limited understanding of the significance of EEG findings it is of particular importance that the degree of probability of the presence and location of an abnormality is expressed in the EEG report.

In order to increase the objectivity of the report we have found it of great value to give a description of the EEG and an interpretation of the significance of the findings without having any other information concerning the condition of the patient. Only after this part of the report has been made other available data concerning the patient are studied and correlated with the EEG findings. This leads to objective reporting, prevents being influenced (and sometimes being misled) by other forms of information, increases the confidence of those requesting the EEG, makes one more alert and has a beneficial influence on teaching. This method usually reveals within a short time that much more objective and valuable information can be derived from the EEG than either the requesting physician or the electro-encephalographer had expected.

IN CONCLUSION

It can be stated that electro-encephalography is now an established method of investigation of the brain with known possibilities and limitations. The improvement of other methods and the advent of new techniques does not diminish its value. On the contrary, in combination with these methods much better information concerning the condition of the brain is obtained. Echo-encephalography is particularly useful in combination with EEG. In most cases suspected of having a cerebral lesion it is possible to arrive at a proper diagnosis in an outpatient consultation with the neurological examination, skull x-rays, an EEG and an echo-encephalogram. This is not only of importance for the early diagnosis of cerebral tumors but not less for the exclusion with a high degree of probability of the presence of such a lesion in the much larger group of patients suspected of but not suffering from an intracranial space occupying lesion.

SUMMARY

The value of electroencephalography amidst the increasing number of procedures for the diagnosis of cerebral lesions is considered. The main types of EEG abnormalities are mentioned, their relative importance is discussed and certain aspects of technique are stressed. Important factors determining the type and degree of EEG abnormalities appear to be the speed with which the lesion develops and the degree to which the cerebral circulation is affected. The importance of correlation and integration of the EEG finding —first evaluated independently— with the results of all methods of investigation is stressed. In this connection echo-encephalography and gamma encephalography are briefly discussed. Two cases histories serve to illustrate these considerations.

RESUMEN

El autor considera el valor de la electroencefalografía dentro del cuadro del creciente número de procedimientos para el diagnóstico de las lesiones cerebrales. Se mencionan los principales tipos de anomalías en el EEG, se discute su importancia relativa y se subrayan algunos aspectos técnicos. Entre los factores que determinan el tipo y grado de las anomalías son importantes la velocidad con que se desarrolla la lesión y el grado en que se ve afectada la circulación cerebral. Se subraya la necesidad de la correlación e integración del resultado del EEG —en principio evaluado independientemente— a los resultados de todos los métodos de investigación. A este respecto se discuten brevemente la eco-encefalografía y la gamma encefalografía. Para ilustrar las precedentes consideraciones se presentan dos casos.

RÉSUMÉ

On discute la valeur de l'electroencéphalographie dans le cadre du nombre croissant de méthodes pour le diagnostic des lésions cérébrales. Les anomalies les plus importantes de l'EEG son mentionnées, on discute leur importance relative et on souligne certains aspects techniques. Parmi les facteurs les plus importants dans la détermination des anomalies de l'EEG se distinguent la vitesse avec laquelle une lésion cérébrale se developpe et le degré d'affection de la circulation cérébrale. On souligne l'importance de la corrélation et intégration du résultat de l'EEG, évalué d'abord indépendamment, avec les données des autres méthodes d'investigation. En rapport avec ceci on discute brièvement l'echoencéphalographie et la gamma encéphalographie. Deux cas sont présentés comme illustration.

ZUSAMMENFASSUNG

Der Wert der Elektroenzephalographie im Rahmen der zunehmenden Anzahl von Methoden zur Diagnostik von Hirnlaesionen wird besprochen. Die Haupttypen von EEG-Stoerungen werden kurz genannt, ihre relative Bedeutung wird eroertert und bestimmte technische Aspekte werden benachdruckt. Zu den wichtigen Faktoren, die die Art und das Ausmass der EEG-Abweichungen bestimmen, gehoeren an erster Stelle die Geschwindigkeit mit welcher sich eine Laesion entwickelt und der Grad der Beeintraechtigung der Hirnzirkulation. Es wird besonders hingewiesen auf

die Notwendigkeit, die EEG-Befunde — nachdem sie erst unabhaengig von anderen Daten ausgewertet sind — mit allen anderen Befunde zu vergleichen und zu integrieren. In diesem Zusammenhang werden die Echo-Enzephalographie und die Gamma-Enzephalographie kurz eroertert. Schliesslich wird das Besprochene an zwei Krankengeschichten erlaeutert.

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Therapeutic Utilization of Radioactive Isotopes in Pituitary Surgery

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During the course of the last fifteen years the therapeutic utilization of radioactive isotopes in pituitary surgery has undergone a considerable development and diversification. One reason for this has been the widening of the scope of available radioactive elements. In addition to Radon 222, which was first utilized, we have seen the introduction of radio-gold Au 198, Phosphorus 32, Yttrium 90, and later Tantalum 182 and Iridium 192. The use of these different isotopes, each one having somewhat different biological effects, has permitted the application of this treatment to a wide scale of problems, from localized destruction of the anatomically normal pituitary gland to interstitial irradiation of pituitary adenomas with voluminous retro- and suprasellar extension.

Experience with the first applications of such focal radiotherapy has shown that while spectacular results may be achieved —even in very advanced cases or poor surgical risks— use of high doses of irradiation close to functionally important brain structures requires special precautions. Partly as a result of such experience we have learned that, contrary to previous belief, cerebral tissue is particularly sensitive to radiation Special stereotaxic surgical techniques therefore had to be developed to insure a high degree of precision. Special attention must also be paid to the limits of tolerance of nervous tissue to the particular kind of radiation utilized.

Several neurosurgical centers have already accumulated wide experience in this domain, which has made it possible to draw certain conclusions regarding the principles, the indications and the limits of the various kinds of interstitial isotope treatment. It has progressively become clear that the seemingly seductive simplicity of such treatment is only apparent.

One should distinguish two separate uses of isotopes in pituitary surgery. One may wish to achieve a complete local necrosis of tissue —hypophysectomy— or the aim may be to subject certain areas to interstitial radiotherapy, either to decrease glandular hyperactivity (for example in Cushing's syndrome or malignant exophthalmos) or to treatment of pituitary tumors. Depending on the aim of the isotope treatment, beta or gamma radiations are used.

During the period from 1954 to 1962 approximately 350 patients were treated by intrasellar isotope application at the Hôpital Sainte-Anne in Paris. The isotopes used were radio-gold Au 198, Yttrium 90 and Iridium 192 (for characteristics see Table I). The operations were carried out first by cerebral stereotaxic equipment adapted to pituitary surgery, using the nasal route; since 1959 a specially-designed apparatus has been used (see below). For suprasellar approach cerebral stereotaxic equipment was used.

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TABLE I

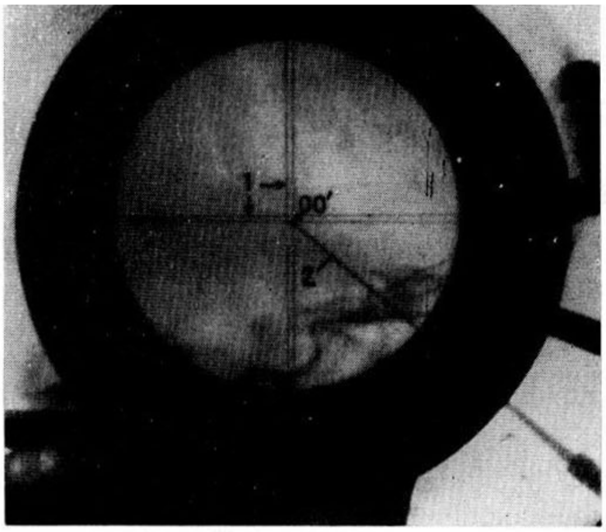
Some physical characteristics of gamma emittor isotopes used in interstitial irradiation

Element	Half life	Energy in MeV	
		Beta	Gamma
Au 198	2.7 days	0.96	0.41
Ir 192	74 days	0.52 and 0.66	between 0.29 and 0.88
Ta 182	115 days	0.36, 0.44, 0.51	between 0.06 ans 1.23
Co 60	5.2 years	0.31	1.17 and 1.33

Selective destruction of the pituitary gland by beta-emitting isotopes. Focal dose of radiation necessary to produce acute necrosis of the hypophysis has been estimated to correspond to 100,000 - 140,000 rads; the sensitivity of neighboring structures, such as oculomotor nerves, optic chiasma and hypothalamus, limits the admissible upper level of radiation reaching these structures to approximately 5,000 rads. External X-ray irradiation or interstitial gamma therapy cannot achieve such spatial selectivity at a radio of 20 : 1, so that the use of beta radiation characterized by a very steep absorption curve becomes necessary. The isotope Yttrium 90 emitting exclusively beta radiation was proposed for hypohysectomy by Rasmussen, Harper & Kennedy in 1953. The physical characteristics of this isotope are a half-life of 64 hours and the emission of 2.4 MeV beta radiation. It is available as Yttrium oxide (Y_2O_3) compressed at high temperature to small cylindrical or spherical seeds. Specific activity of these seeds is generally between 0.5 to 5 mc.

In water or in soft tissue the 2.4 MeV electrons have a maximum range of 11 millimeters, but 99 % of the radiation is absorbed in the first 4 millimeters. The biological action of the very small quantity of secondary radiation (Bremsstrahlung) is negligible; this secondary radiation, however, facilitates the control measurements before implantation. The extremely high doses at the surface of the seed —about 10^7 rads for 1 mc— decrease very rapidly in relation to distance, the level of 100,000 rads (corresponding roughly to the necrotizing dose) being reached at a distance of 3 to 4 mms. Within one more millimeter the dose falls below 20,000 rads. Histological characteristics of the tissular lesion produced by Y 90 seeds reflect such dosimetry; the central necrotic area is extremely clear - cut, the histologically damaged but not necrotized surrounding band being less than 1 mm wide. Dimensions of necrosis vary relatively little in relation to specific activity; in order to enlarge the radius of the lesion by one millimeter, about ten times higher activity is necessary. The final extent of necrosis is attained in approximately 7 to 10 days, during which nearly all the irradiation is delivered. Necrotized tissue is then slowly absorbed, leaving a cavity after the lapse of several months. The size of the lesion is thus mainly a function of the dimension of the seed: the limit between normal and necrotic tissue is situated at a distance of 2 to 4 millimeters from its surface. By adequate disposition of seeds, it is possible to create lesions of a shape corresponding to the target structure, e. g. the pituitary gland.

Theoretically, a complete hypophysectomy can be obtained by symmetrical placement of two seeds of 1 mc on either side,



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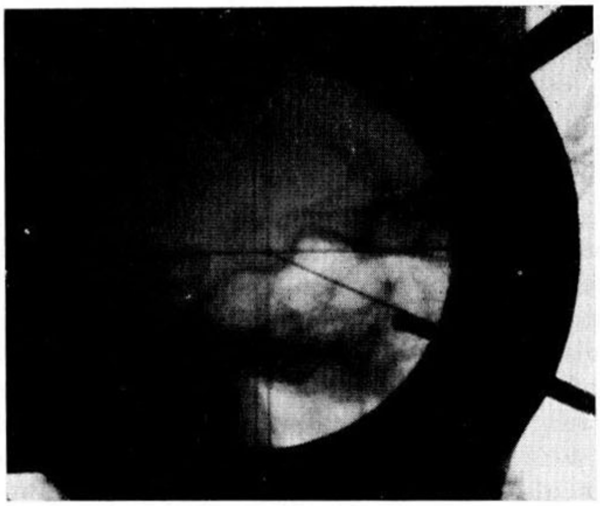

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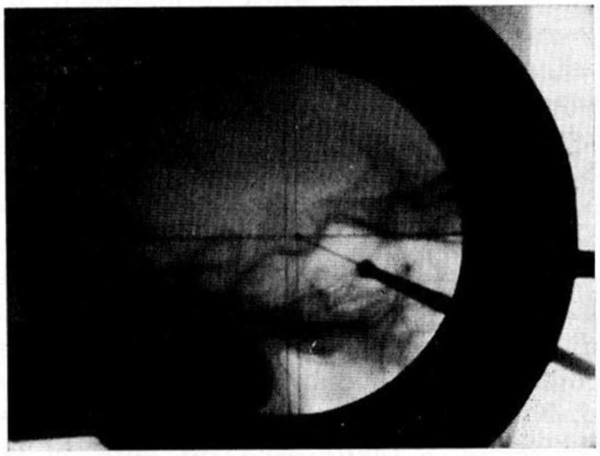

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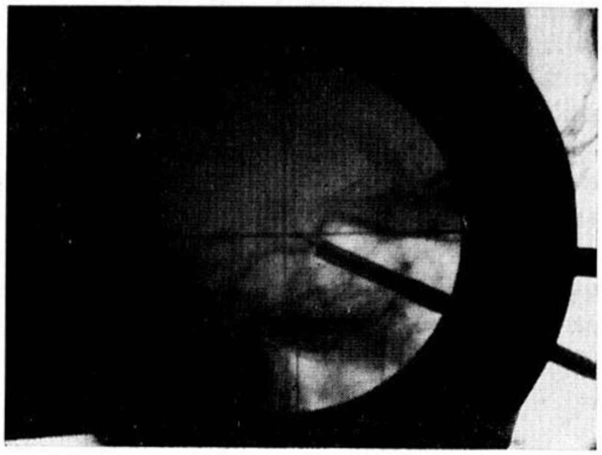

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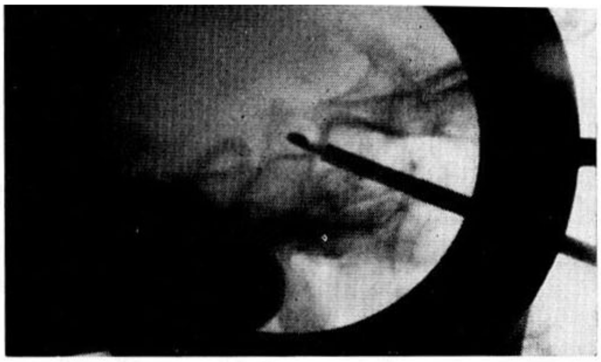

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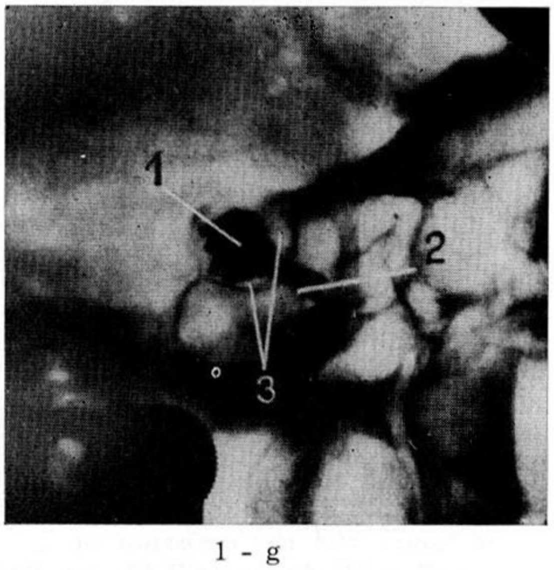

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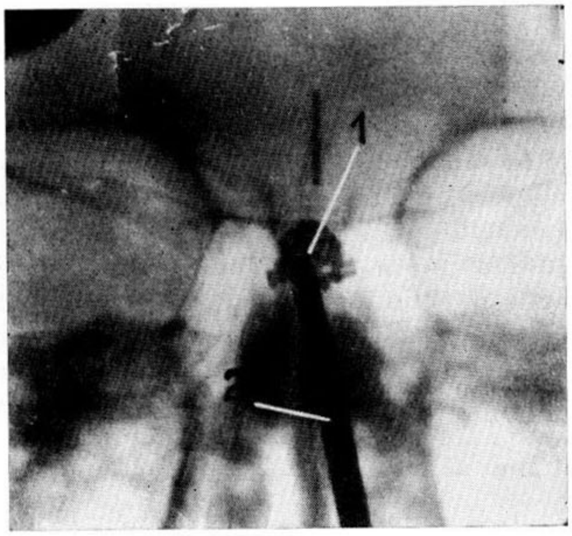

1 - h

Fig. 1 a - h — *X-ray pictures of an Y90 hypophysectomy (see text).*

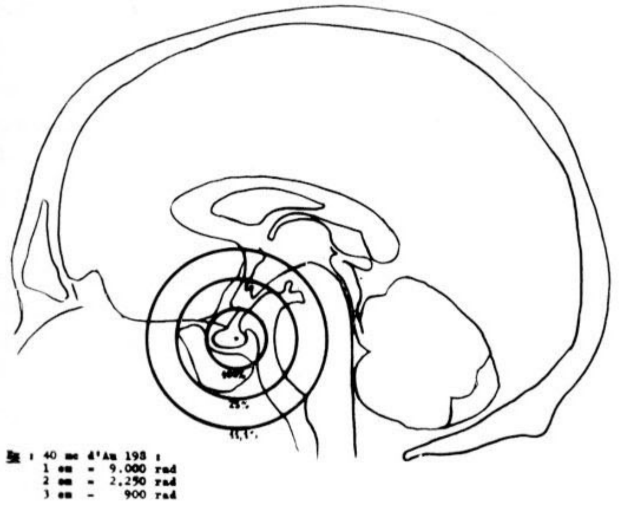

Fig. 2. — *Isodose-lines in intrasellar implantation of a punctiform gamma-ray source. Mid-sagittal section.*

in such a manner that the borders of the necrosis produced by each will join; but such a solution presupposes a precision difficult to obtain in practice. Moreover, the content of the cavernous sinus may be exposed to heavy irradiation in case of a slight lateral displacement. For this reason we prefer to fill the sella turcica with 20 to 30 small seeds (1 × 1.5 mm) of lesser activity (0.10 - 0.20 mc/seed), the rounded bulk of the seeds occupying the center of the gland (Fig. 1 g-h). The implantation of Y 90 requires precise stereotaxic techniques, accompanied by repeated X-ray controls. Once introduced, the isotope destroys the surrounding structures irremediably. The radioopacity of the seeds evidently facilitates such control.

Radiation protection of personnel is relatively simple, since the beta rays are absorbed by a 1 cm layer of water. On the other hand the relatively brief period reduces the risk of contamination of the instruments or surgical clothing by crumbling of the seeds.

It is evident that one could hardly use beta radiation in treatment of tumors, where the relatively extensive target volume would necessitate an excessive number of very closely-placed seeds because of their small field of necrotizing action.

Application of gamma ray emitting isotopes. In pituitary surgery the field of gamma ray-emitting isotopes coincides with that of external radiotherapy, to which it is closely related and from which it differs principally by its focal concentration. The doses delivered by a punctiform source diminish in space according to the square of the distance: if the dose at 1 cm corresponds to 100 %, at two centimeters there will be only 25 %, at three 11 %, etc. This permits delivery of a high-level irradiation in the neighborhood of the source, the dose received by adjacent tissues decreasing rapidly (Fig. 2).

One readily sees the advantages of such a geometrical distribution in the treatment of well-localized, circumscribed tumors of moderate size, surrounded by vulnerable functionally important or vital structures.

Recent data on cerebral radio-biology underline the importance of this fact. The classic treatise "Histopathology of irradiation" of Snider-Bloom (1948) still considered nervous tissue as particularly radioresistant. However, in the course of the last few years, several studies, particularly the thorough analyses of Zeman, Arnold and Lindgren, have progressively determined the threshold values of delayed cerebral radionecrosis, establishing the fact of particular sensitivity of the brain to irradiation. Although the results obtained by different authors are not directly comparable because of the differences in the type of radiations utilized, it has become clear that the white matter of the brain, as well as the hypothalamus or the optic chiasma, undergo progressive histological alterations — even to the extent of necrosis — following an irradiation of 5/6,000 rads per 30 days (X rays of 2-400 KV).

On the other hand, experience has shown that efficacious treatment of most brain tumors necessitates local doses of this level or even higher, which explains the importance of the focal character of isotopes irradiation.

Interstitial gamma therapy is currently utilized in cancerology, where a wide experience has been accumulated. Its physical and radiobiological bases, as well as the techniques of application in different organs, have been to a great extent elaborated and codified (cf. 13, 14, 57).

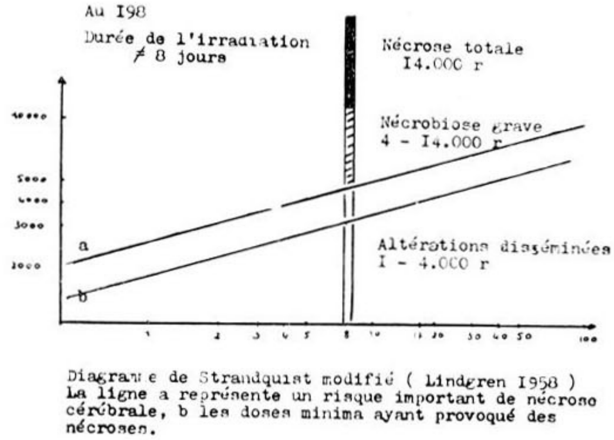

Fig. 3 — *Threshold values of doses producing late radionecrosis of brain. Vertical axis: doses in "r", horizontal axis: duration of radiation treatment in days (logarithmic representation). Line a): great probability of secondary necrosis; line b): lowest doses having provoked necrosis (Lindgren, 1958). The vertical column shows the anatomo-dosimetric correlation found in late necrosis following implantation of Au198 (Vedrenne, Szikla, Talairach, 1961).*

These rules, however, must be adapted to the particularities of the special field represented by the brain; recent knowledge concerning radiosensitivity of nervous tissue as well as the surgical possibilities of interstitial application must be taken into consideration.

The possibilities, the indications and the limits of intracranial isotope implantation are essentially determined by dosimetric and surgical considerations.

A. *Dosimetric considerations.* The introduction of gamma sources in a sensitive and highly differentiated organ such as the brain requires first of all a precise dosimetry. To be able to avoid the consequences of overdosage on adjacent structures it has been necessary to determine reactions of the normal nervous tissue to isotope irradiation. In order to establish the limits of cerebral tolerance we undertook a study of cases of intracerebral implantation of radioactive gold, where late necrosis appeared several months, often years, later. This study concerned particularly 13 brains of this group where we could compare clinical evolution and histological image with dosimetry. The result was the following:

1) above 12 - 14,000 rads, delayed necrosis was homogeneous and total.

2) between 4 - 5,000 and 12,000 rads grave tissue alterations were found, consisting of partial necrosis of structures with a glial reaction more or less important according to localization.

3) between 1,000 and 4,000 rads sporadic alterations were encountered, especially around blood vessels, imbedded in tissue of normal appearance.

These values correspond very nearly to the doses given by the diagram of Lindgren (Fig. 3). Thus in the intracranial implantation of gold 198, the isodose of 4,000 rads should not reach structures in which secondary damage should be avoided. On the basis of this striking correspondence it can be admitted that in a general way the values delimited by the dose/time diagram can be applied to the dosimetry of other gamma-emitting elements, the half-life of which differ from that of gold.

Thus for instance in the case of intrasellar application of radio-gold the dose attaining the optic chiasma should not be higher than 4,000 rads. It is relatively easy to calculate the number of millicuries one may introduce in function of distance without serious risk of late visual complications.

We would like to emphasize the role played by the effective duration of irradiation in determining the threshold values of necrosis. Thus the admissible dose level in short-time irradiation is relatively low; we feel that frequent brain necrosis observed after intracerebral cobalt 60 applications lasting only a few hours is largely imputable to the time factor. On the other hand, one may attain higher doses without the risk of delayed necrosis by the use of long-living isotopes such as Ir 192 or Ta 182. It is possible to combine various elements, e. g., radio-gold Au 198 and Iridium 192.

B. *Surgical considerations.*

Within the limits imposed by sensitivity of neighborhood structures, the distribution of sources is conditioned by the surgical possibilities of implantation. The aim is to realize the most homogeneous irradiation

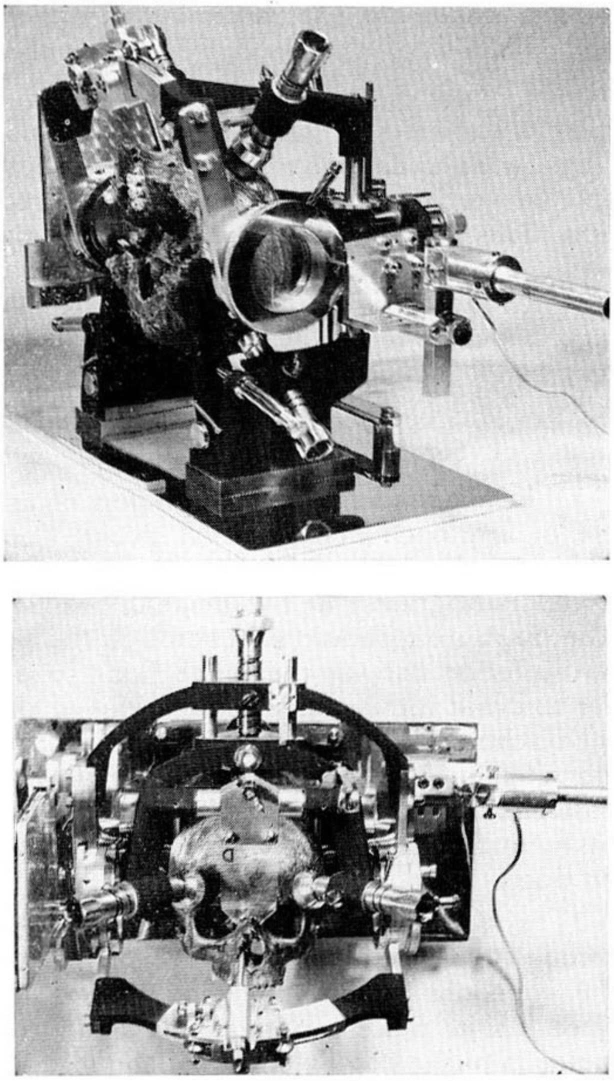

Fig. 4. — *Stereotaxic apparatus used in pituitary surgery (for description see text).*

possible of the target volume with the greatest possible precision and with the least possible trauma.

The technical solution capable of reconciling these partly contradictory requirements will be determined mostly by the particular seat of the tumor mass.

In pituitary stereotaxic surgery one may utilize one (or possibly two) trocars introduced either by the nasal or the transcerebral route. However, the target volume may vary from that of a normal hypophysis through that of an enlarged sella in acromegaly to that of the considerable volume of certain pituitary adenomas. A single implanted source may satisfactorily irradiate the content of the normal sella, but in the treatment of voluminous pituitary tumors such limitations on surgical approach may result in a rather unhomogeneous irradiation of the neoplasm. In order to resolve this difficulty we introduce somewhat longer radioactive wires. The use of special trocars permits placement at different angles to trajectory of the trocar. Thus one may achieve different geometrical dispositions and thus adapt dosimetry to the individual case.

In those cases where the dimension of the tumor mass surpasses the technical possibilities of implantation or would necessitate excessively high doses —which according to our experience occurs above 30 to 35 cm^3— one may combine external radiotherapy with subsequent interstitial irradiation.

Stereotaxic technique and results

A) Interstitial isotope applications cannot be achieved by a simplified surgical act. Consequences of imprecision in isotope placement, though often invisible in the immediately postoperative period, will become manifest after several weeks or months (sometimes years). To understand the sources of the principal complications and the resulting technical necessities, some anatomical facts must be taken into consideration:

a) the great variability of form and volume of the sella are well known. Repartition of radioactive products should always take into account such individual variations.

b) the optic nerves and chiasma are not sufficiently protected by the more or less open dural diaphragm of the sella turcica; implanted material may easily find its way into the basal cistern, particularly during filling of the sella with Y 90 seeds. It is therefore necessary to limit the placement to a line passing from the posterior clinoids to the tuberculum sellae, i. e. approximately 3 mm below the level of the anterior clinoids. Higher-placed seeds may cause damage to the optic chiasma, producing visual field defects, or cause lesions of the

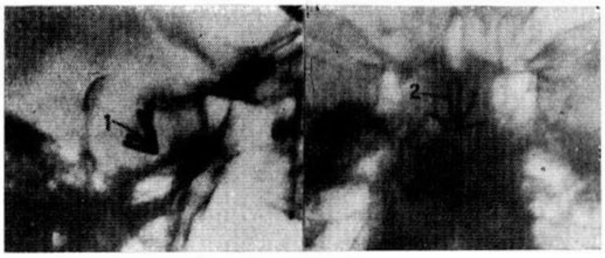

Fig. 5. — *Anteroposterior and lateral view of gold implantation in eosinophile adenoma (35 mc of Au 198).*

pituitary stalk with consequent diabetes insipidus.

c) oculomotor nerves seem to be protected by the fibrous wall of the cavernous sinus, but in fact seeds may easily traverse the dural membrane. If the roof of the sphenoid sinus is visible in the a-p X ray pictures, this may indicate the lateral limits that should not be transgressed by the seeds. Otherwise one may adopt the more or less arbitrary limit of approximately 5 millimeters from midline on either side.

d) intrasellar prolongation of subarachnoid space (—"intrasellar cistern"—) extends more or less downwards and communicates more or less openly with the basal cistern. Even a small trephine opening of 2 mm may permit postoperative CSF leakage, with consecutive meningeal infection. Moreover, advanced decalcification of the base of the skull, intra-pituitary metastases, and necrotizing action of irradiation may play a role in the apparition of this complication. It therefore becomes necessary to close the orifice of introduction in the floor of the sella hermetically. We proposed the use of a metallic screw at the Bruxelles congress in 1957; after several modifications we now complete screw implantation by injection of liquid bone-wax in the small burr-hole.

During the 2 years since the introduction of this technique we observed CSF leakage in only one case, with radiological evidence of local metastasis, five months after operation.

B) The stereotaxic equipment used for pituitary surgery is composed of two parts (Fig. 4):

a) a stationary part allowing centering and fixation of the head by five rubber tipped rods;

b) a semicircular arc having at its ends rings with radio-opaque crosspieces movable in vertical and antero-posterior direction. The arc supports a movable carriage with a guiding tube, so constructed that any introduced instrument will attain the target, whatever the angle of introduction may be.

C) The operation is executed in five steps (cf. fig. 1 a-h):

1) localization and determination of angle of approach of the target point. Centering of the arc on the sella is controlled by teleradiography or by image-intensifier. The trephining should pass through the antero-inferior part of the sellar floor in order to avoid intrasellar prolongations of the subarachnoid space. The direction of the trocar should follow the greatest antero-posterior diameter of the pituitary to facilitate intrasellar disposition of radioactive products.

2) a 3,5 mm trephine is introduced through one nostril to the anterior wall of the sphenoid sinus, which is then perforated. In its place a tube of the same diameter is pushed to the floor of the sella.

3) inside this sterile tube a small caliber trephine (2,5 mm) is introduced and then perforates the floor of the sella.

4) the implantation-trocar is introduced in the sella and radioactive material is implanted, having regard to the criteria referred above. X-ray pictures check the position of the seeds or wires.

5) obturation of the trephining hole (see above).

The operation is carried out under general anesthesia. The whole procedure lasts about one to one and a half hours.

The immediate post-operative course is usually simple. The patient may leave his bed in two to four days after the operation. Body temperature usually does not mount higher than 38° C.

D) Technical aspects of Y 90 hypophysectomy and clinical results.

TABLE II

Complications and mortality in 145 cases of Y 90 hypophysectomy for metastatic breast cancer (1959-61). Age: 25 to 73 years.

Operative mortality (1-15 *days*)	*CSF leakage*	*Visual field defects*	*Oculomotor paresis* (*unilateral*)
6	7	3	2
1 troubles of coagulability (roentgentherapy +++)	(death from meningitis: 2)	2 unilateral	
2 advanced hepatic metastases (jaundice)	5 decalcifications of sella	1 bitemporal hemianopsia	
2 cachectic general state 1 cardiac failure during anesthesia: pulmonary metastases.	2 pituitary metastases		

Preoperative selection excluded only patients with advanced brain metastases (papilloedema) hepatic metastases (jaundice) and pleuropulmonary metastases (contraindicating general anesthesia).

TABLE III

Therapeutic effects of Y 90 hypophysectomy in metastatic breast cancer. 145 cases, age: 25 to 73 years

1 — Effect on diffuse pain:	
Immediate disappearance of pain	80%
Painless after 3 months	50%
2 — Effects on objective signs:	
Recalcification of bone metastases	33%
Disappearance of pulmonary metastases	3%
Cicatrization of local ulcerations	2%

The physical characteristics of this isotope require a particularly precise technique. To achieve complete hypophysial destruction we introduce 20 to 40 seeds of 1 × 1.5 millimeters, filling the center of the sella having regard to the above-mentioned anatomical criteria (Fig. 1). We prefer utilization of small rods or spheres of 1 mm diameter to the use of longer cylindrical seeds, the latter having a tendency to push each other further and eventually into the cavernous sinus.

Of a total of 287 hypophysectomies for metastatic breast cancer, Tables II and III summarize data concerning 145 cases operated on in 1959-1961. Therapeutic results (Table III) correspond roughly to those published by other authors.

E) Interstitial irradiation of the pituitary in malignant exophthalmos and Cushing's syndrome.

Radiation therapy is often used to diminish pituitary hyperactivity after medical treatment has failed to do so. Unlike hypophysectomy only non-necrotizing doses are given in the order of three thousand to five thousand rads.

As is shown by Fig. 2, gamma ray emittors are appropriate for such irradiation and permit safeguarding of neighboring structures. One may thus avoid the risk of late complications inherent in transcutaneous radiotherapy. External X-ray therapy cannot deliver such doses to the pituitary without heavy irradiation of sensitive juxtasellar structures.

The genesis and treatment of malignant edematous exophthalmos are still controversial. Inefficiency of medical treatment may necessitate a surgical decompression of orbital cavities. Antehypophysial origin of exophthalmos is generally admitted, but conclusive evidence is still lacking to show whether the reason is to be attributed to a modification of the sensitivity of receptors to TSH or to some other principle associated with TSH. Many authors emphasized efficiency of pituitary irradiation in this sometimes dramatic condition. Utilization of isotopic irradiation was obviously at hand.

Ten cases have been operated by our team. Exophthalmos was accompanied by moderate or frank hyperthyroidism in some cases. In 4 patients Y 90 hypophysectomy was carried out at the request of the endocrinologic department. In the other cases radioactive gold seeds were introduced into the sella with a total activity of 15 to 25 mc.

Immediate results were satisfactory in all cases with regression of retrobulbar edema, disparition of oculomotor paresis and complete recovery of visual acuity in the two cases with signs of optic neuritis.

We have only partial information on late results. Patients of the Y 90 groups are said to have a marked pituitary hypofunction — a natural consequence of hypophysectomy. Excellent results were obtained with two cases operated with radio-active gold, the results lasting 4 and 5 years respectively. The observation periods of the other four cases are too short to allow final judgment, but the early results are encouraging.

Twelve patients with Cushing's syndrome were operated on in our department by radioactive gold implantations, two in 1957, two in 1958, one each in 1959-1960 and 1961, three in 1962 and two in 1963. There was no case of mortality. We observed one case of late complications due to excess of radioactivity (35 mc). About ten months after operation a marked hypopituitarism led to a mental confusion which disappeared after adequate substitution therapy was introduced. At the same time an important visual field defect appeared, which did not, however, interfere with professional activity.

Obesity, erythrosis and hirsutism were remarkably influenced. In the 3 cases with severe vascular pathology, the effect of the

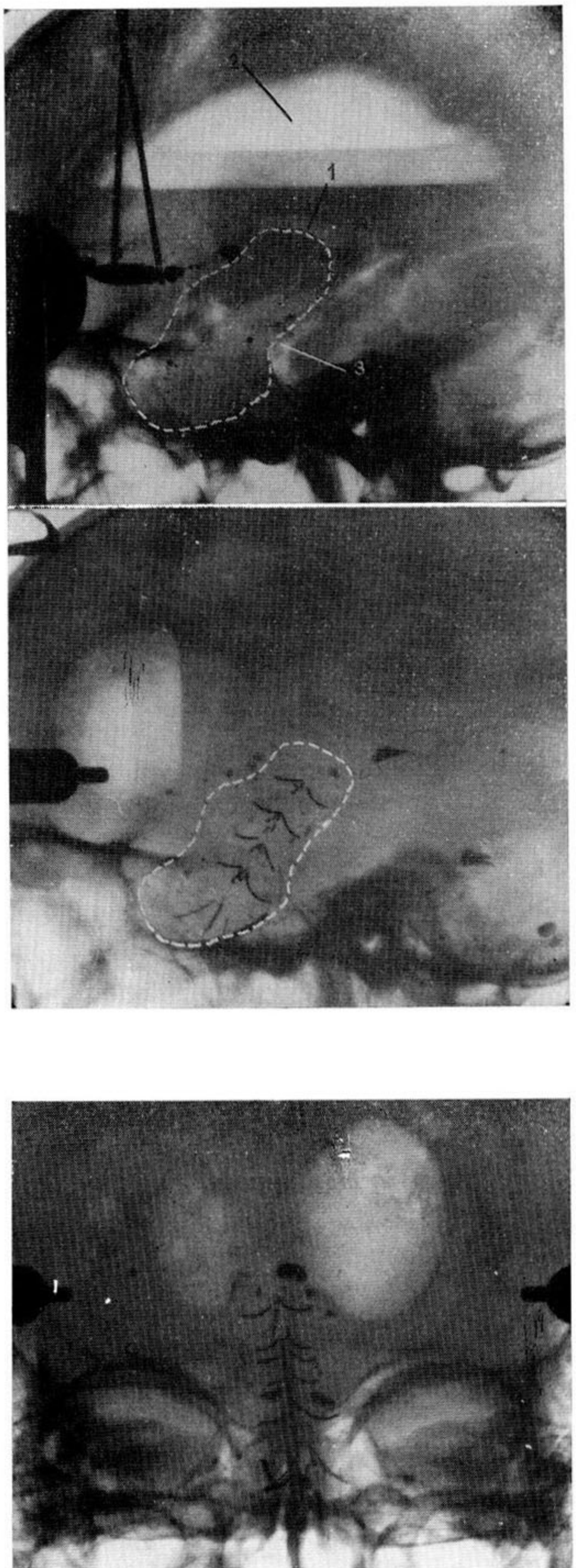

Fig. 6 a - b — *Lateral and anteroposterior X-ray pictures of iridium 192 implantation in extrasellar chromophobe adenoma (4,6 Mc).*

treatment on this syndrome was rather mediocre. Sexual potency was restored in the two males; in one case of amenorrhea and two others with irregular bleedings menstrual cycles became normal.

All patients except for the case mentioned above are leading normal lives without substitutive therapy.

Thyroid tests, urinary 17 cetosteroid and 17 oxycorticoid excretion are within normal limits; there exists, however, some evidence of latent pituitary hypofunction, as shown by dynamic tests.

F) Interstitial irradiation of pituitary adenomas.

Total activity and geometrical disposition of implanted radioactive material depend on the volume and the spatial configuration of the tumor. In small adenomas, irradiation delivered by one or two intrasellar sources introduced by the nasal route may be considered satisfactory. However, as dose level falls off rapidly in function of distance, supra or retro-sellar masses cannot be sufficiently irradiated in this way. Thus it becomes necessary to introduce the isotopes in such extensions by the transcerebral-frontal, parietal or temporal-way. Different solutions are illustrated by the figures 5 and 6 a-b.

Clinical results may be resumed in the following:

a) eosinophile adenomas.

Till January 1961, 23 cases (14 males and 9 females) were treated by intrasellar application of radioactive gold. Four of them have had previous craniotomy, seven were treated by X-ray therapy. Nine of them had radiological evidence of supra-sellar spread. Average age was 46 years, one patient was 65 and another 70 years old. Four patients had severe arterial hypertension (240/120 Hg mm), five have been diabetic. Postoperative observation period was 1 to 7 years.

There was no surgical mortality; one patient, having a "giant" adenoma, died 3 months later following a frontal craniotomy performed because the previous intrasellar implantation failed to improve her state.

Of the 22 cases, 20 had complete or satisfactory relief of headache and diffuse pain. Ten have been ameliorated from the morphological point of view, five of them to a surprising extent.

Of the eleven cases with visual field defect, eight have been ameliorated, in one case there has been aggravation.

Fourteen patients could return to normal social and professional life.

In no case was it necessary to give hormonal substitutive treatment. Sexual potency became normal in three males. Diabetes disappeared in two cases out of five.

b) Chromophobe adenomas.

In the first period patients have been referred to isotope treatment mostly because it was impossible to operate them in the usual way, in consequence of advanced age, very poor general health, and important retrochiasmatic tumor spread. Favourable experience contributed to extend the field of indications.

Radioactive gold implantations were carried out in 35 patients, 20 males and 15 females. Average age was 47 years in males (21 to 70 years), 54 years in females (20 to 74 years). Five patients have already been operated by transfrontal craniotomy, five have had previous radiotherapy. Eight cases had an important retrochiasmatic development, three had a "giant adenoma".

In this series postoperative mortality was rather high, 5 patients, i. e. 13 %. Cause of death has been intratumoral bleeding (1 case) cardiac failure during anesthesia (1 case) radiation lesion of hypothalamus and brain stem (2 cases), unknown in 1 case. All these patients had important retrosellar tumor-extension. One more patient died after craniotomy undertaken four months later because of aggravation of the ocular symptoms.

In one of the two cases of post-irradiation brain necrosis death followed a second radioactive gold implantation, three years after the first. Erroneous interpretation of pneumo-encephalography led us to suppose a regrowth of the tumor; post-mortem examination of the brain showed hypothalamic and pontine lesions due to heavy irradiation.

Sometimes it may be rather difficult to determine whether secondary aggravation should be imputed to tumor--growth or to

TABLE IV

Clinical results of radioactive gold implantation in 28 chromophobe adenomas

	cases	evolution unknown	stationary	aggravation	amelioration	complete recovery
bitemporal hemianopsy	13	3	1	2	3	4
bitemporal hemianopsy + amaurosis of 1 eye	7	—	2	—	5	—
homonymous lateral hemianopsy	2	—	—	—	2	—
paracentral scotomas	3	—	—	—	1	3
normal visual fields	3	—	2	1	—	—
visual acuity						
normal	6	—	6	—	—	—
impaired	15	—	5	—	10	—
1 eye blind	7	—	5	—	2	
hypopituitarism						
slight or none	17	—	17	—	—	—
marked	6	—	2	2	2	—
grave	5	—	3	—	2	—
diabetes insipidus	—	—	—	1 (transitory)	—	—

Professional activity: return to normal activity: 14 (9 males, 5 females).

Gonadic functions: amenorrhea was definitive in all cases. Impaired libido and sexual potency returned to normal in 4 cases, ameliorated in 2.

late consequences of irradiation. In the first period we inclined to suppose rather the insufficiency of isotope application; experience has shown that it is necessary to procure conclusive evidence concerning the existence of a neoplastic mass.

In another case subsequent craniotomy three months after implantation was well supported.

Follow-up has been short in 4 patients (4 to 6 months); in the 24 other cases observation period was 2 to 6 years. Table IV resumes data of 28 patients.

Indications of isotope treatment in pituitary adenomas.

Multiple factors should be taken into consideration:

a) volume and localization of the adenoma.

1. Intrasellar adenomas with slight or no impairment of visual fields. We consider them as very good indications; eosinophile adenomas are certainly the best cases. Hormonal disorders seem to be influenced favourably without serious secondary hormonal deficit.

2. Secondarily extrasellar adenomas with visual signs.

—Cases with moderate or anterior supra-

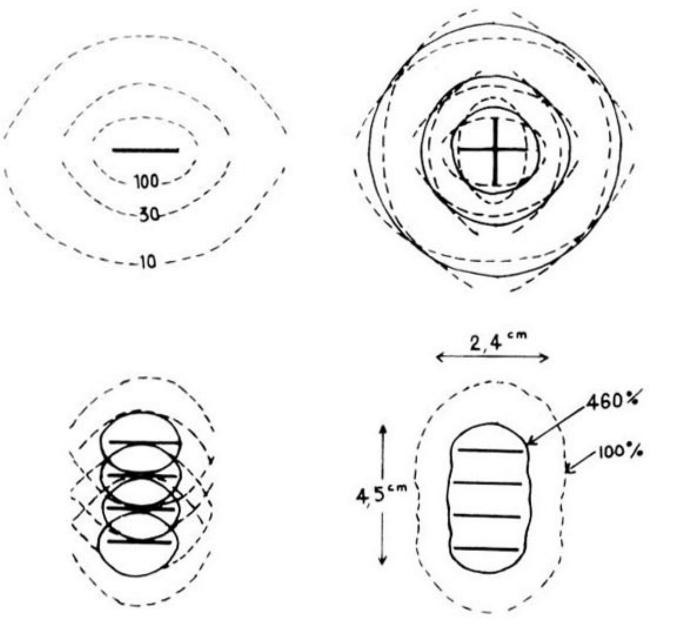

Fig. 7. — *Dosimetric scheme of a four-level crossed implantation of gamma emittor wires in a cylindrical volume.*

sellar extension represent the classical field of surgery; isotope treatment, however, may equally give very satisfactory results.

—Adenomas with retrosellar spread.

Difficulties encountered during surgical extirpation grow with posterior development, because of uneasy access, adhesion of tumor to the walls of the third ventricle etc. On the other hand, nasal stereotaxic implantation is generally well supported, technically simple and gives a fairly good and lasting result. According to our opinion such cases should be referred first to isotope treatment.

—Adenomas with very important suprasellar extension ("giant adenomas"). In these cases it is obviously impossible to deliver sufficient doses to the whole tumor mass by nasal implantation only. Using the transcerebral route it may become possible to distribute sources in a rather homogenous way, particularly if the neoplasm has a more or less cylindrical form (Fig. 6 a-b). For treatment of tumors above 30-35 cm^3 or presenting evidence of irregular upper and especially lateral spread, we feel that the more diffuse distribution of doses by external radiation therapy is more adequate, although tumor doses must be kept at a comparatively low level.

b) In cases where open surgery is contraindicated because of advanced age or poor general health, radioactive implantation may still be carried out, if general anesthesia can be supported. On the other hand, some of our patients refused open surgery, but accepted radioactive implantation. Such psychological factors as well as the above mentioned medical considerations may equally play a role in the choice of isotope treatment.

CONCLUSIONS

1. Therapeutic application of radioactive isotopes in pituitary surgery has been developed considerably in the course of the last 15 years. Accumulated long-range experience permits to delimit the field of indications and the limits of this treatment.

Pituitary applications of intense focal irradiation delivered by radioactive isotopes requires precise placement of sources by special stereotaxic techniques.

2. Radioactive implantation of the pituitary may aim at selective destruction of glandular tissue as in hypophysectomy or the aim may be interstitial radiotherapy as in pituitary tumors or in some forms of pituitary hyperactivity; beta or gamma emittors are correspondingly utilized.

3. By its limited necrotizing effect, exclusive beta radiation of Yttrium 90 permits to achieve selective destruction of the pituitary gland, without damaging adjacent structures. Utilization of gamma-ray emittors is contraindicated in this purpose, as they cannot attain such spatial selectivity.

4. Interstitial radiotherapy by implantation of gamma-sources is particularly indicated in deepseated well localized and limited target-volumes; one may thus deliver locally high doses without exceeding the tolerance-limits in surrounding sensitive structures.

5. Geometric disposition of sources has to be adapted to each case by a carefully established dosimetry taking into consideration surgical possibilities as well as the threshold values of late irradiation necrosis of the brain.

SUMMARY

After discussing the physical and radiobiological principles of radioactive implantation treatment, the authors describe the various modalities of stereotaxic technique used by them in pituitary implantations of radioactive material (Y 90, Au 198, Ir 192).

Clinical results of Yttrium 90 hypophysectomy in metastatic cancer (145 cases) as well as those of interstitial gamma-therapy in Cushing's disease (12 cases), malignant exophthalmos (10 cases) acromegaly (23 cases) and chromophobe adenomas (35 cases), operated between 1954 and 1961 are presented.

RESUMEN

Después de discutir los principios físicos y radiobiológicos del tratamiento mediante la implantación de material radioactivo, los autores describen las diversas modalidades de la técnica estéreotaxica usada por ellos en implantaciones de material radioactivo en la pituitaria (Y 90, Au 198, Ir 192).

Son presentados los resultados clínicos de la hipofisectomía con Ittrium 90 en casos de cáncer metastático (145 casos), así como también de gammaterapia intersticial en casos de enfermedad de Cushing (12 casos), exoftalmia maligna (10 casos), acromegalia (23 casos), y adenoma cromófobo (35 casos), operados entre 1954 y 1961.

RÉSUMÉ

Après avoir discuté les principes physiques et radiobiologiques du traitement avec une implantation radiactive, les auteurs décrivent les différentes types de téchnique stéréotaxique qu'ils ont employé pour des implantations pituitaires de matériels radiactifs (Y 90, Au 198, Ir 192).

On présente des résultats cliniques d'hypophysectomie avec Ittrium 90 dans des cas de cancer méthastatique (145 cas) ainsi que ceux de gammathérapie interstitiale dans des cas de maladie de Cushing (12 cas), exophtalmie maligne (10 cas), acromégalie (23 cas) et adénome chromophobe (35 cas), opérés entre 1954 et 1961.

ZUSAMMENFASSUNG

Nach der Besprechung der physikalischen und radiobiologischen Prinzipien der Behandlung mit radioaktiven Nadeln, beschreiben die Autoren die verschiedenen Modalitaeten ihrer stereotaxischen Technik fuer die Einfuehrung radioaktiven Materials (Y 90, Au 198, Ir 192) in die Hypophyse.

Es werden die klinischen Ergebnisse der Hypophysektomie mit Yttrium 90 bei Karzinommetastasen (145 Faelle) sowie die Ergebnisse der interstiziellen Gamma-Therapie beim Morbus Cushing (12 Faelle), malignem Exophtalmus (10 Faelle), Akromegalie (23 Faelle) und chromophoben Adenomen (35 Faelle), die zwischen 1954 und 1961 operiert worden sind, besprochen.

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Cerebral Implantation of Radio-Active Material

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Recent interest in the implantation of radioactive material in the brain is to a large extent associated with the development of stereotaxic surgery. R. H. Clarke (1908), the originator of the stereotaxic method of surgery, realized some of the potentialities of his invention. More than 40 years ago, writing from the Laboratory of Pathological Chemistry at University College, London, he speculated on its surgical application to sections of tracks in the brain and to the treatment of cerebral tumours, as be said, "by the introduction of tubes or needles of radium". The stereotaxic instrument lends itself to the introduction of isotopes in suitable form and has been used for three main purposes:

a) Interstitial irradiation of certain cerebral tumours.
b) Pituitary ablation.
c) The production of lesions in the treatment of Parkinson's disease and allied conditions.

This paper will deal with the first two subjects and will present the author's personal experience and a review of the literature.

Interstitial Irradiation of Cerebral Tumors

The treatment of cerebral tumours by orthodox radiotherapy has been disappointing in the great majority of cases, but there are certain characteristics of interstitial irradiation which increase its effectiveness in brain tumours. The choice of isotopes giving rise to beta or gamma emittors or to varying proportions of both is made in regard to their physical properties. The advantage of beta particles lies in their low penetration and makes them particularly suitable where neighbouring structures must be protected from irradiation. These conditions apply particularly in irradiation of the hypophysis with its close relationship to the optic chiasma, the oculomotor nerves in the wall of the cavernous sinus and the hypothalamus. However, their low penetration renders the beta emittors quite inadequate for tumours of large volume. The gamma particles with their greater range are therefore appropriate for the larger hemisphere tumours. Au 198 at low dosage has a penetration of beta rays in water or in soft tissues amounting to no more than 1.5 - 2 mm. but at higher dosage (above 20 mC) the volume of destruction is increased, due to the gamma particles, and

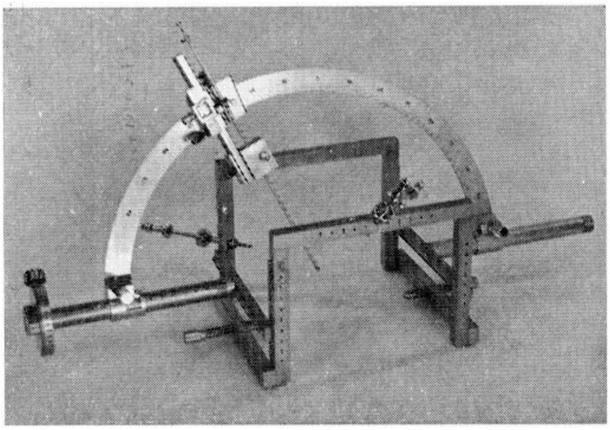

Fig. 1. — *Leksell's stereotaxic instrument showing the rectangular frame with radio-opaque markings and the semicircular "electrode" carrier.*

is also surrounded by an intermediate area of necrobiosis 1 - 2 cm. in width. The changes in this latter area are also progressive over a number of months. Similar changes follow the use of the gamma emittors of long half-life, namely Ta 182, Ir 192, Co 60. Yttrium 90 however, is a pure beta emittor, its range being limited to a few mms. in brain tissue with valuable applications in hypophyseal surgery.

However, in general it seems unlikely that tumours of a diameter greater than 4 cm. can be effectively treated by interstitial irradiation as shown by the dosimetric calculations of Dutreix [5] (1961). The alternative to external irradiation involves partial surgical removal of the tumour followed by implantation of isotopes into the tumour bed, as described by Talairach and his co-workers [23, 24] (1961). In this situation gamma emittors of long half-life, (Ir 192 or Ta 182) have the advantage of activity over a long period with high penetration. It is probable that with high dosage of a large volume of brain tissue, the risk of serious necrosis and oedema is increased by employing the short half-life emittors such as Co 60 or Au 198, with the application of the greater part of the dose within a period of a few hours or a few days respectively. In addition the low activity of Ir 192 and Ta 182 increases the safety of personnel handling isotopes during surgical procedures. Becker and Scheer [1, 2] (1953) described an ingenious method of irriadating tumour cavities by the use of Co 60, in which the isotope is incorporated in small pellets suspended in an inactive liquid in an elastic container of appropriate size. As a refinement of this method variations in the specific gravity of the supporting liquid were made so as to concentrate the isotope activity in different parts of the cavity. The container is then removed after the calculated dose has been applied.

Mundinger [11, 12] (1956 & 1958) and Mundinger and Riechert [13] (1962) have reported on the average survival of patients with a variety of tumours of the cerebral hemispheres treated by interstitial irradiation by isotopes and compared with similar groups treated by orthodox external irradiation. A hundred and twenty one patients were involved in this series and were treated between 1954 and 1959. These workers employed a variety of techniques and isotopes, and in their hands they achieved a significant improvement in the survival rate, namely 46.9 % of patients subjected to combined surgical and radio-isotopic treatment against the survival of 29.2 % in the group treated by operation and X-ray therapy. There appeared to be a relationship between the length of survival and the particular isotope used, the localisation of the tumour and the tumour dosage. In the glioblastomas, for instance, the longest survival periods were seen in the frontal tumours following radio-cobalt irradiation,

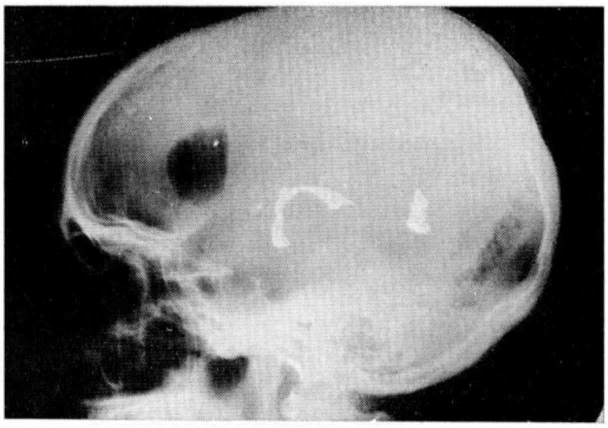

Fig. 2. — Case 1. *Tumour of the third ventricle outlined by myodil (pantopaque). Lateral view supine.*

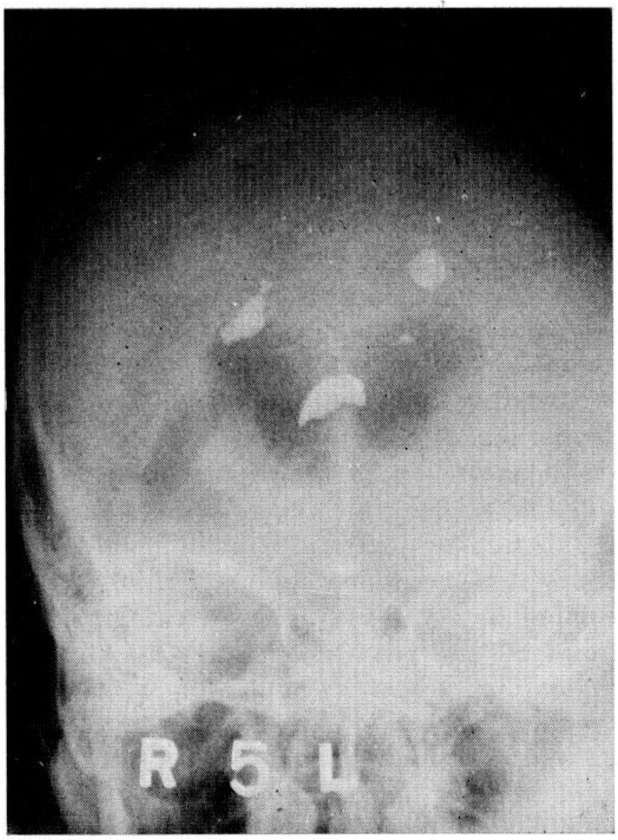

Fig. 3. — Case 1. *Corresponding antero-posterior view. Myodil lying on upper surface of tumour.*

an average tumour dosage of 10,000 - 13,000 r being necessary. They conclude that longer survival periods in the undifferentiated gliomas can be achieved by combined surgical and interstitial radio-isotopic treatment (especially with radio-cobalt) as compared with surgical and X-ray therapy. The survival rate (which is nearly twice as high as in X-ray treatment) shows a significant relationship to the average amount of tumour dosage and tumour localisation. Also it is pointed out that the period of treatment is thus shortened by three quarters or two thirds of the time required for orthodox X-ray therapy.

In our clinic we have found that small (2 - 3 cms. diameter), surgically inaccessible, but strategically placed, tumours are best suited to interstitial irradiation (Hankinson, 1961). In practice, these are tumours well outlined radiologically in relation to the third ventricle and are either anatomically "pinealomas" posteriorly, or craniopharyngiomas anteriorly. Small rods (3 mms. by 0.8 mm.) of Au 198 of dose 1 - 2 mC introduced by Leksell's stereotaxic instrument (Fig. 1), (Leksell, [10] 1959) and distributed symmetrically in the tumour have proved satisfactory. The dosage and distribution are planned to provide 7,000 to 10,000 rads. Tumours involving the posterior part of the third ventricle have yielded the best results with loss of physical signs and reduction of intracranial pressure. Six of these patients are alive and apparently well six years, four years, two years (two) and one (two) years after such treatment.

Three representative cases will be described. The first, six years ago, was a man in his thirties suffering from severe headaches, vomiting and ocular palsies and showing papilloedema and bilateral extensor plantar responses. Positive contrast ventriculography revealed a large tumour in the posterior part of the third ventricle (Figs. 2 & 3). This was implanted with Au 198 giving a dose of 7,000 rads. For the first three days he became increasingly drowsy and then suddenly his condition improved and he made a good recovery. He resumed work and has continued his career as an accountant.

The second patient is a young man of 19 who complained of thirst, anorexia and the loss of 20 lbs. weight during the previous three months. He had also recently lost

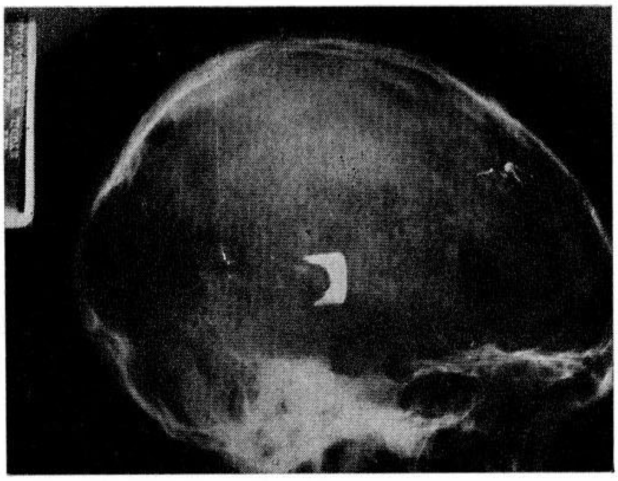

Fig. 4. — Case 2. *Supine lateral view of myodil outlining anterior portion of third ventricle tumour. Note flecks of tumour calcification.*

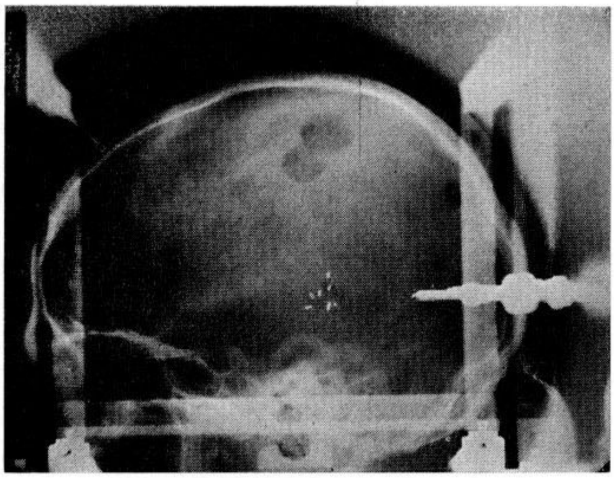

Fig. 5. — Case 2. *Operative radiograph of gold seeds in position.*

libido and needed to shave every third day only. Apart from wasting and weakness he had no physical signs. The positive findings were low ketosteroids and some flecks of abnormal calcification in the midline of the skull in the pineal region. He was not suffering from diabetes insipidus and an initial diagnosis of anorexia nervosa was abandoned. Lumbar air encephalography showed a filling defect in the posterior part of the third ventricle and this was confirmed by myodil (pantopaque) which would not pass down the distorted aqueduct (Fig. 4). During the next four weeks he was given hydrocortisone and Nilevar (an anabolic agent) his general condition improved very much and he gained weight. Nevertheless it seemed reasonable to attempt to deal with the tumour itself and accordingly nine radioactive gold seeds were introduced giving a calculated tumour dose of 8,500 rads (Fig. 5). He was decidedly drowsy for the first three days after operation and on the second day developed those signs which he might well have shown before, namely, gross nystagmus and complete loss of elevation of his eyes. This disturbance was of short duration and from the fifth day his convalescence continued uneventfully. However, his symptoms recurred a year later and he died soon afterwards. Histologically the tumour, which had infiltrated anteriorly, was diagnosed as a pineocytoma.

The third case was that of a woman of 36 who presented with severe headaches for two months, more recently accompanied by vomiting. Her only sign was severe papilloedema with retinal haemorrhages and exudates. Ventriculography revealed a spherical filling defect in the posterior part of the third ventricle, in the midline but not obliterating the supra-pineal recess. The upper end of the aqueduct was displaced downwards and forwards by approximately 1 cm. from its normal position and was completely blocked to both air and myodil. Torkildsen's procedure was carried out on the same day and she was relieved of her headaches and vomiting for three months. She was then readmitted to hospital mith recurrence of symptoms, a left hemiparesis and marked occulo motor

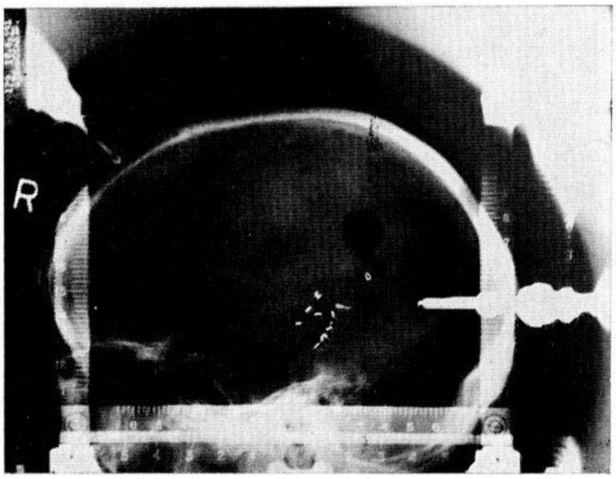

Fig. 6. — Case 3. *Operative radiograph of gold seeds in position. Lateral view.*

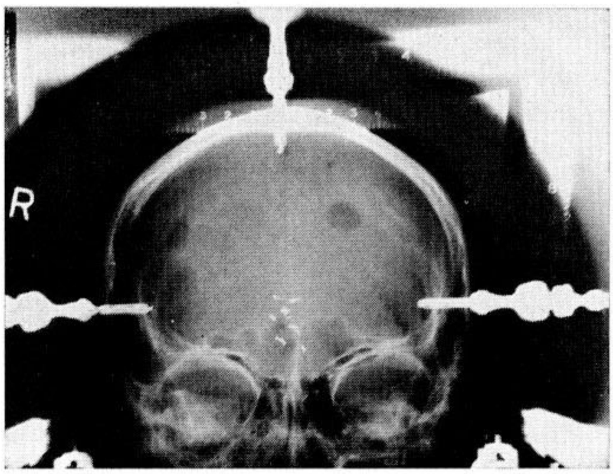

Fig. 7. — Case 3. *Corresponding antero-lateral view.*

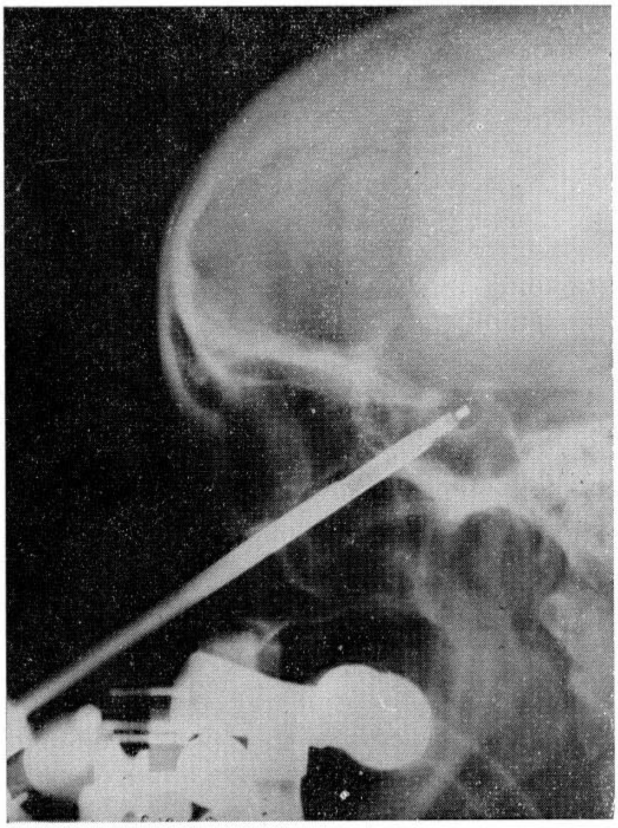

Fig. 8. — *Operative view of nasal, trans-sphenoidal introduction of yttrium 90 into pituitary fossa. (Forrest's method).*

abnormalities. The pupils were small with no reaction to light or to accommodation. She was unable to elevate or to depress her eyes and there was gross nystagmus. At this stage twelve rods of Au 198 were inserted into the tumour giving a calculated dose of 7,500 rads (Figs. 6 & 7). For 48 hours the patient was very drowsy, but on the third day she became much more alert and had no headache. On the next day, quite suddenly, her eye movements returned and immediately appeared to be equal and normal with full elevation and depression. Her left hemiparesis rapidly improved and at the end of a week she was walking well. She has been seen at three monthly intervals for two years. Her fundi returned to normal and so far she has remained well.

These cases showed a decrease in size of the tumour following interstitial irradiation and re-opening of the aqueduct. They also suggest a very significant swelling during the 72 hours following the implantation and this factor should exclude pituitary tumours showing any degree of chiasmal involvement. This may also apply to the solid craniopharyngiomas and the results in our small series have not been as satisfactory as with the "pinealomas". As regards the cystic craniopharyngiomas, it is a simple enough matter to replace the fluid with radioactive colloidal material (Wycis et al. [26] 1954) and this is probably the treatment of choice. However, the use of hypothermia and hormonal replacement therapy may justify a more radical approach to these troublesome lesions.

The pituitary adenomas can be treated by the combination of a beta and gamma emittor (Y 90 and Au 198) (Tournoux [25] 1958). This is indicated in the treatment of the hormonal disturbances of the eosinophilic and basophilic adenomas and in cases of chromophobe adenomas and craniopharyngiomas unsuitable for surgical decompression by reason of their posterior extension or the patient's poor general con-

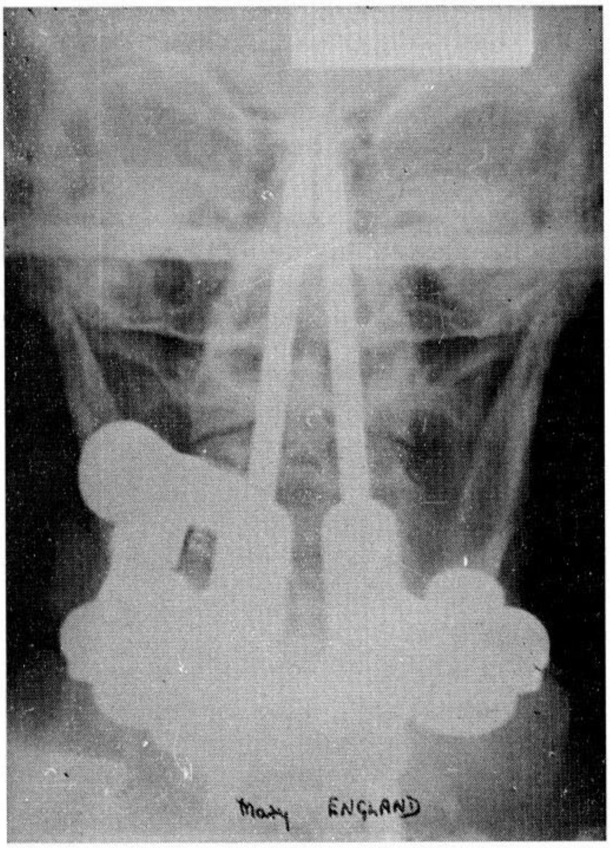

Fig. 9. — *Corresponding antero-posterior view showing trocars in position.*

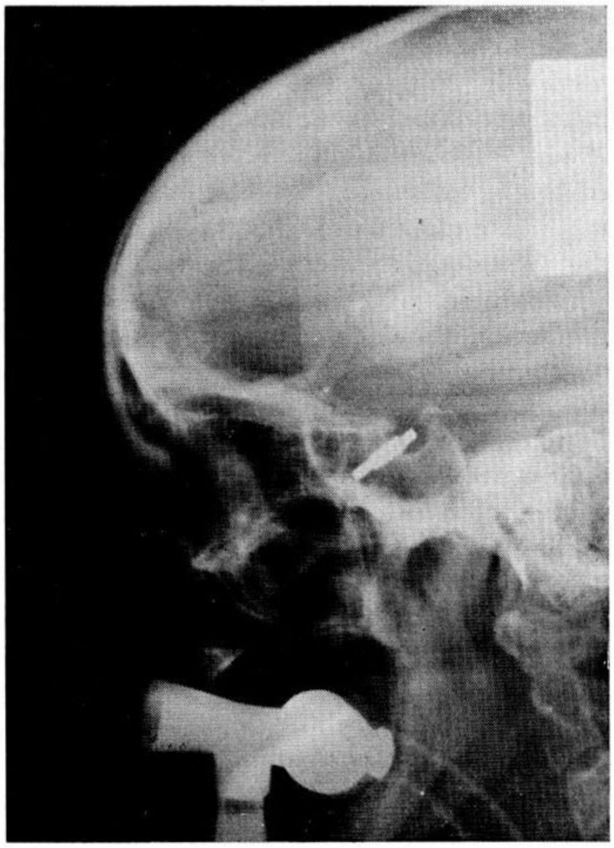

Fig. 10. — *Final view of nylon capsules (containing yttrium 90) in position (superimposed). - Supporting metal screw maintains capsule's position and plugs defect in floor of fossa.*

dition. Usually those cases presenting with visual field defects are better treated by high voltage radiotherapy with or without preceding surgical decompression (Mundinger & Riechert [13] 1962).

Pituitary Ablation

Destruction of the pituitary by irradiation has been performed for the alleviation of hormone dependent metastases, for the ocular and renal lesions of advanced diabetes mellitus and for some endocrine states resulting from pituitary over-activity (Rothenberg et al. [21], 1955; Riechert [15], 1956; Gleadhill [7], 1959; Notter [14], 1959 Riechert & Mundinger [20], 1960). Many of the patients with metastatic carcinoma and all the diabetics for whom pituitary ablation is recommended are in every way poor risks for major surgical procedures. It is reasonable, therefore, to employ the closed trans-sphenoidal introduction of isotopes to open surgical hypophysectomy, if comparable results can be obtained.

Pituitary ablation has been performed in association with our colleagues of the Department of Radiotherapy on one hundred and twenty patients since 1956 - since 1959 by the method of Forrest of Glasgow (Forrest et al. [6] 1959) (Figs. 8, 9 & 10). Most of these operations have been for metastatic mammary carcinoma but twelve have been for diabetes, three for acromegaly and three for Cushing's syndrome. Three substances have been used viz. radon, Y 90 and Au 198. Each emits gamma and beta particles in different proportions. Irrespective of the degree of irradiation the energy of gamma particles accords with the inverse square law but the beta emission falls off so rapidly at 3 - 4 mms. from its source in

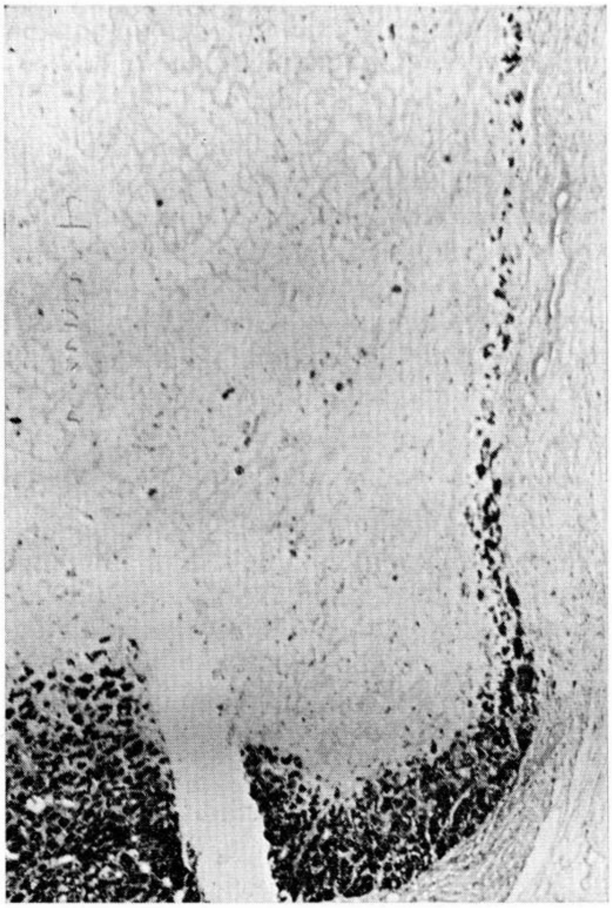

Fig. 11. — *Section of pituitary after yttrium 90 implantation showing almost complete necrosis except for a thin rim of surviving cells.* — Dosage 4.5 mC x 2 producing 12 — 14,000 rads.

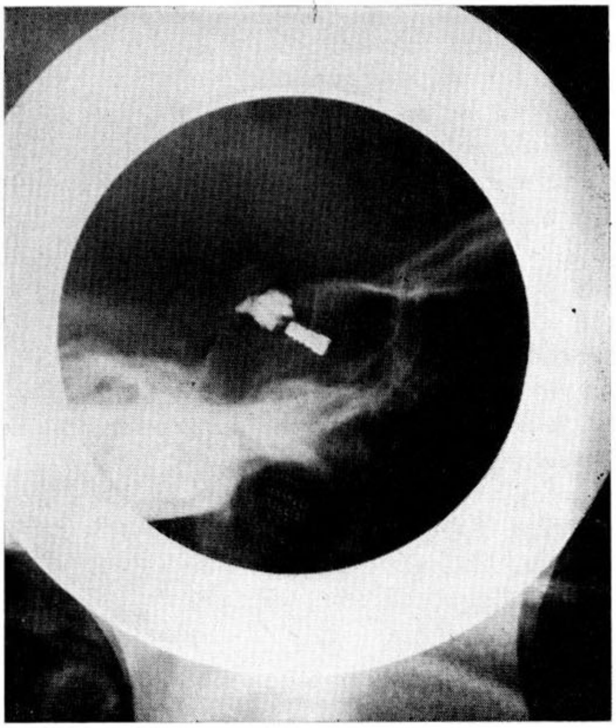

Fig. 12. — *Pituitary ablation by trans-sphenoidal "packing" of fossa by yttrium 90 seeds (Talairach's method).*

brain or pituitary, that beyond this range there is no tissue damage. Thus in relation to the size and shape of the pituitary fossa and the proximity of the optic chiasma, Y 90 being predominantly a beta emittor, is preferable to radon, which produces a much higher proportion of gamma particles. Au 198, which lies between the two in this respect, is being used at present in relatively low dosage to produce partial cell destruction in acromegaly.

The metastatic cases have been unselected in the sense that poor general condition was not a contra-indication — and some of the patients were very ill indeed. The diabetics were, of course, all suffering from the severe renal or retinal damage or both of the Kimmelstiel-Wilson syndrome. All the more recent patients, including the diabetic and hormonal cases, have had pre- and post-operative studies to estimate the degree of pituitary destruction. Reduction in iodine uptake and the necessity for thyroid replacement therapy have indicated satisfactory ablation in these cases. Two symmetrical sources of Y 90 of 4.5 mC each were implanted, producing a total irradiation of 12 - 14,00 rads (Fig. 11). Of the 120 cases, 12 sustained some degree of visual disturbance, usually a few months later. Transient ptosis occurred in two cases; polydipsia, usually transient, in 12 cases and C.S.F. leak in five cases. Talairach (1955) [22] (Fig. 12) uses numerous small sources of Y 90 introduced by the trans-sphenoidal route and for completeness of ablation it may be that this is the most satisfactory solution to the problem of hypophysectomy by irradiation.

SUMMARY

The indications for the use of interstitial irradiation by radioactive isotopes are considered under the following headings:

a) Hemisphere tumours.
b) Midline tumours.
c) Pituitary adenomas.
d) Hypophysectomy.

Hemisphere tumours

These have been treated by partial excision and followed by implantation of radioactive sources into the tumour bed, or direct implantation without surgical excision. In the latter case it has been demonstrated that this type of irradiation is unsuitable for tumours of diameter greater than 4 cm. Beyond this limit external irradiation is preferable. However, Mundinger and his associates have shown an improved prognosis in certain classes of hemisphere tumours treated by interstitial irradiation.

Midline tumours

The group most suitable for interstitial irradiation consists of the small, strategical-

ly placed tumours which are obstructing the C.S.F. circulation and can usually be well outlined radiologically. The are the craniopharyngiomas anteriorly and the "pinealomas" posteriorly, and also occasionally tumours on the clivus. Many of these are of course surgically inaccessible except by stereotaxic technique. The results in six of these cases are described using radioactive gold (Au 198).

Pituitary adenomas

The experience of Talairach, Mundinger and Riechert are described. The results in the hormonal state of these tumours have been satisfactory. The use of this technique in the presence of visual field defects is still in doubt.

Hypophysectomy

The techniques of hypophysectomy by implantation of radioactive gold (Au 198) or yttrium (Y 90) are described. The indications are in the treatment of hormone dependent metastases in carcinoma of the breast and in the Kimmelstiel-Wilson syndrome of diabetes mellitus. There has been a small incidence of complications due to infection from C.S.F. leakage, and by inadvertant irradiation of neighbouring structures such as the optic chiasma and the nerves in the walls of the cavernous sinus.

Interstitial irradiation of certain selected tumours is a powerful and sometimes very successful technique but requires correspondingly accurate methods of placement and dosage estimation in accordance with the general principles of radiotherapy.

RESUMEN

Las indicaciones para el uso de radiaciones intersticiales por medio de isótopos radioactivos fueron analizadas bajo los siguientes subtítulos:

a) Tumores hemisféricos.
b) Tumores medios.
c) Adenomas pituitarios.
d) Hipofisectomía.

Tumores hemisféricos

Estos tumores se tratan por medio de una excisión parcial seguida por la implantación de fuentes radioactivas en la zona afectada, o por medio de la implantación directa prescindiendo de la excisión quirúrgica. En este último caso, se ha demostrado que este tipo de radiación es inadecuado para tumores de un diámetro mayor de 4 cm. Más allá de este límite es preferible la radiación externa. Sin embargo, Mundinger y sus colaboradores han demostrado que es posible un pronóstico más acertado en ciertas clases de tumor hemisférico tratadas por radiación intersticial.

Tumores medios

El grupo más adecuado para la radiación intersticial es el de los tumores pequeños, estratégicamente situados, que obstruyen la circulación del L.C.R. y que pueden ser localizados en general radiológicamente. Se trata de los craneofaringeomas en la parte anterior y de los "pinealomas" en la parte posterior, y a veces también de tumores en el clivus. Naturalmente muchos de ellos son quirúrgicamente inaccesibles excepto por la técnica estereotáxica. Los resultados de seis de estos casos han sido descriptos mediante el uso de oro radioactivo (Au 198).

Adenomas pituitarios

Se describen las experiencias de Talairach, Mundinger y Riechert. Los resultados en el estado hormonal de estos tumores han sido satisfactorios. El empleo de esta técnica en presencia de defectos en el campo visual es todavía puesto en duda.

Hipofisectomías

Las técnicas de hipofisectomía por implantación de oro radioactivo (Au 198) ó Itrio (Y 90) han sido descritas. Se dan indicaciones para el tratamiento de metastasis de origen hormonal en carcinoma del seno y en el síndrome de Kimmelstiel-Wilson de la diabetes mellitus. Se ha observado la incidencia de complicaciones debidas a infecciones provenientes de pérdidas de L.C.R. y radiaciones involuntarias a las estructuras circundantes, como por ejemplo el quiasma óptico y los nervios de las paredes del seno cavernoso.

La radiación intersticial de determinados tumores es una técnica poderosa y a veces muy eficaz, pero requiere métodos rigurosamente exactos en la localización y estimación de la dosis, de acuerdo con los principios generales de la radioterapia.

RÉSUMÉ

Les indications d'emploi d'irradiations interstitielles d'isotopes radioactifs sont considérées sous les titres suivants:

1. Tumeurs hémisphériques.
2. Tumeurs médiales.
3. Adénomes hypophysiaires.
4. Hypophysectomie.

Tumeurs hemisphériques

On les a traités par excision partielle, suivie par l'implantation de Sources radioactives dans la couche de la tumeur, ou par implantation directe sans excision chirurgique. Dans le dernier cas on a démontré que ce type d'irradiation ne convient pas aux tumeurs ayant plus de 4 cm. de diamètre. Cette limite dépassée la radiotherapie externe est preferable. Cependant Mundinger et ses associés ont démontré un meilleur prognostique dans certaines classes de tumeurs hémisphériques traités par radiothérapie interstitielle.

Tumeurs médiales

Ce groupe est celui qui se prête le mieux à la radiotheérapie interstitielle; il est constitué par de petites tumeurs placées stratégiquement qui obstruisent la circulation de L.C.R. et dont le contour peut etre apprécié radiographiquement. Ce sont des craniopharyngiomes dans la partie antérieure et des "pinéalomes" dans la partie postérieure, et parfois des tumeurs dans le clivus.

Adénomes hypophysiaires

L'expérience de Talairach, Mundinger et Riechert est exposée. Les résultats concernant l'état hormonal des tumeurs est satisfaisant. On n'est pas sùr sur l'emploi de cette technique quand il y a des défauts du champ visuel.

Hypophysectomie

La technique d'hypophysectomie par l'implantation d'or radioactif (Au 198) ou Ittrium (Y 90) est exposée. Les indications sont pour le traitement de métastases d'origine hormonale des mamelles et pour le syndrome de Kimmelstiel-Wilson dans la diabetes mellitus. Seulement dans peu de cas il y a eu des complications dues à l'infection causée par la perte de L.C.R. et à l'irradiation involontaire de zones voisines telles que le chiasma optique et les nerfs des parois du sinus caverneux.

L'irradiation interstitielle est dans certaines especes de tumeurs une technique puissante et effective mais demande des méthodes appropriés quant au placement et à l'estimation de la dose d'accord avec les principes généraux de la radiothérapie.

ZUSAMMENFASSUNG

Die Indikationen für eine Anwendung der intracavitären (interstitiellen) Bestrahlung durch radioaktive Isotopen wird unter folgenden Gesichtspunkten betrachtet:

a) Tumoren der Hemisphären.
b) Tumoren in der Mittellinie.
c) Adenome der Hypophyse.
d) Exzision der Hypophyse.

Tumoren der Hemisphären

Diese wurden mit einer partiellen Exzision und nachfolgender Implantation radioaktiven Materials in das Tumorbett behandelt oder mit direkter Implantation ohne chirurgische Exzision. In letzterem Falle konnte gezeigt werden, dass diese Art der Bestrahlung für Tumoren mit einem grösseren Durchmesser als 4cm unzulänglich ist. Für grössere Tumoren ist eine Bestrahlung von aussen vorzuziehen. Trotz alledem konnten Mundinger und seine Kollegen zeigen, dass sich in gewissen Gruppen von Tumoren der Hemisphären die Prognose nach intracavitärer Bestrahlung bessert im Vergleich mit der orthodoxen Bestrahlung von aussen.

Tumoren der Mittellinie

Unter diesen sind die Tumoren, welche die Zirkulation der cerebrospinalen Flüssigkeit obstruieren und welche sich radiologisch gut darstellen lassen, am besten für die intracavitäre (interstitielle) Bestrahlung geeignet. Zu diesen Tumoren gehören die anterior gelegenen Kraniopharyngeome und die posterior liegenden Pinealome sowie gelegentlich Tumoren, die auf dem Klivus liegen. Viele dieser Tumoren können chirurgisch nicht entfernt werden ausser durch die stereotaktische operative Technik. Die Resultate in 6 Fällen nach radioaktiver Goldbehandlung (Au 198) werden beschrieben.

Adenome der Hypophyse

Die Erfahrungen von Talairach, Mundinger und Reichert werden beschrieben. Die Resultate bezüglich der hormonalen Aktivität dieser Tumoren sind Zufriedenstellend. Ein Erfolg nach Anwendung dieser Technik bei Fällen mit Sehfelddefekten erscheint zweifelhaft.

Exzision der Hypophyse

Die Methoden der Hypophysenexzision durch Implantation von radioaktivem Gold (Au 198) oder Yttrium (Y 90) werden beschrieben. Eine solche Behandlung ist indiziert bei Hormon —abhängigen Metastasen von Karzinomen der Mamma und bei dem Kimmelstiel - Wilson Syndrom des Diabetes mellitus. Komplikationen stellten sich nur gelegentlich ein als Folge einer Infektion der Cerebrospinalflüssigkeit Rhinorhoea und als Folge einer unbeabsichtigten Bestrahlung benachbarter Strukturen wie z. B. des Chiasma opticum und der Nerven in den seitenwaenden des Sinus cavernosus.

Die intracavitäre (interstitielle) Bestrahlung bestimmter ausgewählter Fälle stellt eine sehr wirksame und manchmal sehr erfolgreiche Technik dar. Sie verlangt daher aber auch eine genaue Platzierung und Schätzung der Dosis des radioaktiven Materials in Übereinstimmung mit den allgemeinen Prinzipien der Radiotherapie.

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The Treatment of Neoplasms of the Brain and Face, Employing Regional Chemotherapeutic Perfusion and Infusion Techniques

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The term "perfusion" is meant to imply the isolated extracorporeal circulation of one or both carotid arteries and jugular veins in the operating room under general anesthesia. The extracorporeal circuit consists of a mechanical pump, a bubble oxygenator, and a heat exchanger. The vehicle used to prime the pump system is either blood or dextran. The chemotherapeutic agent used in such cases is either dissolved throughout the extracorporeal pumping system or is injected directly into the inflow catheter once the perfusion has begun. Such perfusions usually last 30 minutes. Several different drugs have been used in this series of perfusions: nitrogen mustard, A-139 Cytoxan, phenilalanine mustard, and thio-TEPA.

The term "infusion" implies the continuous intra-arterial injection of a chemotherapeutic agent dissolved in saline or other appropriate diluent. This procedure is begun in the operating room under local anesthesia where a catheter is placed into the carotid artery or a branch thereof. This catheter is in turn connected to a mechanical pump which can be set to deliver a given volume of fluid per unit time at a steady rate. The infusion itself is usually performed in the patient's room over a period of one to five days. The chemotherapeutic agents used for infusions have included Methotrexate, nitrogen mustard, A-139, phenylalanine mustard, Cytoxan, and a sulfur mustard (S-112).

Sixty-two carotid perfusions have been performed since the beginning of this study in 1958. These perfusions have been categorized in Table I. As regards survival time following perfusion, it is of interest that little if any prolongation of survival time was produced in the case of brain tumors. On the other hand, in the case of squamous cell carcinomas perfused via the external carotid artery, six of these 23 cases (26 per cent) are presently living with no evidence of recurrence of their tumor following perfusion. These more favorable results were obtained when regional perfusion was used as an adjunct to definitive surgical excision of the primary lesion.

Sixty-one regional infusions have been followed up to date. A breakdown of these infusions is shown in Table II. No significant therapeutic response or prolongation of survival time occurred in the case of brain tumors. Of the 31 squamous cell carcinomas, 13 are living with evidence of recurrence, one is living with no evidence of recurrence, and 17 have died. The longest follow-up on any living infusion patient is only one year thus far. The use of irradiation along with infusion in the group of patients with squamous cell carcinomas did not appear to affect the survival of the patient: twelve of the dead

TABLE I

Type Perfusion	*Alive* Recurrence	No Recurrence	*Dead*
Common Carotid			
Brain tumors	0	1	15
Others	1	1	3
	—	—	—
Totals	1 (4 years)	2 (1 over 2 yrs.; 1 over 3 yrs.)	18
External Carotid			
Adenocarcinoma	2	0	4
Squamous cell carcinoma	1	6	16
Basal cell carcinoma	0	1	2
Adamantinoma	1	0	0
Melanoma	0	2	2
Sarcoma	0	0	2
Ependymoblastoma	0	0	1
Meningoma	0	0	1
	—	—	—
Totals	4	9 (1 over 1 yr.; 1 over 2 yrs.; 1 over 3 yrs.; 4 over 4 yrs.)	28

TABLE II

Type Infusion	*Alive* Recurrence	No Recurrence	*Dead*
Internal Carotid			
Brain tumors	3	0	10
Others	0	0	1
	—	—	—
Totals	3	0	11
External Carotid			
Adenocarcinoma	0	1	1
Squamous cell carcinoma	13	1	17
Undifferentiated carcinoma	1	0	5
Transitional cell carcinoma	0	0	1
Melanoma	0	1	1
Lethal midline granuloma	0	0	1
Fibrosarcoma	0	0	1
Rhabdomyosarcoma	1	0	0
Adenoacanthoma	1	0	0
Basal cell carcinoma	1	0	0
	—	—	—
Totals	17	3	27

patients and eleven of the patients still living also received irradiation.

Several general statements can be made regarding both perfusions and infusions. No one drug appeared to be more favorable than another as regards prolongation of survival time. As regards face tumors, nitrogen mustard appeared to afford the best relief of pain following regional chemotherapy, probably related to the neurotoxic effect of this drug. This neurotoxicity is primarily a destructive effect upon the myelin of the peripheral nerve fibers, based upon laboratory experiments as well as histological sections from patients[6]. Pain relief was usually associated with gross or histological signs of regression of the primary tumor. Recurrence of pain usually coincided with either gross or histological evidence of further progression of the tumor growth. Several of the anti-cancer agents, such as nitrogen mustard and A-139, were more toxic locally to the normal tissues, producing edema and erythema. In most cases, biopsies have been obtained following regional chemotherapy; histological changes have been observed early after therapy and in some cases are present some months later, even after further growth of the surviving tumor cells is evident [1].

Several technical considerations, such as the leakage of drugs from the regional circulation into the rest of the body and the effect of temperature upon anti-cancer drug activity have been fairly thoroughly worked out. The leakage of anti-cancer agents into the rest of the body is reduced to a minimum by not only virtue of the regional circulation of the drug but also the very rapid uptake of these drugs in the local tissues [2]. The use of hyperthermia has been found to potentiate the effectiveness of anti-cancer agents *in vitro* [3].

SUMMARY

In summary, regional chemotherapeutic perfusion and infusion for brain tumors have failed to significantly alter the natural history of these tumors. Regional perfusion of face tumors has been effective in prolonging survival time when it is used as an adjunct for definitive surgery [4, 5]. The combination of regional infusion and irradiation of face tumors has not yet shown any more beneficial effect than either one alone, although the follow-up period on this group of patients is at present relatively short.

Studies are now underway towards obtaining a more direct method of attack upon the neoplastic cells, utilizing a combination approach employing regional vascular isolation techniques and tumor stroma-specific or tumor parenchyma-specific carriers (antibodies) of therapeutic agents.

RESUMEN

Resumiendo, podemos afirmar que ni la perfusión ni la infusión quimioterapeútica regional han resultado eficaces para alterar el curso natural de los tumores cerebrales. La perfusión regional de tumores faciales ha demostrado ser eficaz en prolongar el plazo de sobrevida en caso de ser utilizada como complemento de la cirugía [4, 5]. La combinación de la infusión regional con la irradiación de los tumores faciales no ha demostrado poseer una acción más efectiva que cada uno de esos métodos por separado.

Se dirigen los estudios actualmente hacia la obtención de un método más directo de ataque a las células neoplásticas, mediante la utilización de técnicas de aislación regional vascular combinadas con vehículos de agentes terapéuticos específicos del stroma tumoral o bien específicos del parénquima tumoral (anticuerpos).

RÉSUMÉ

En résumant, nous pouvons affirmer que ni la perfusion ni l'infusion chimiothérapeutiques locales ont réussi à alterer l'histoire naturelle des tumeurs cérébrales. La perfusion régionale des tumeurs faciales s'est montrée efficace dans la prolongation du temps de survie lorsqu'elle a été employée comme complément de la chirurgie définitive [4, 5]. L'infusion régionale et l'irradiation des tumeurs faciales combinées n'exercent pas une action plus effective que chacune d'elles isolément.

On dirige actuellement les études vers l'obtention d'une méthode d'attaque plus directe aux cellules néoplastiques, en utilisant des techniques d'isolement vasculaire régional, combinées avec l'utilisation de vehicules, spécifiques du stroma tumoral ou bien spécifiques du parenchyma tumoral (anticorps), portant des agents thérapeutiques.

ZUSAMMENFASSUNG

Zusammenfassend hat die regionale chemotherapeutische Perfusion und Infusion keinen Erfolg bei den Hirntumoren gehabt, um die Naturgeschichte dieses Tumors wesentlich zu aendern. Die regionale Perfusion der Gesichtstumoren hat Erfolg gehabt, indem sie die Ueberlebenszeit verlaengert hat, wenn sie zusaetzlich zur endgueltigen chirurgischen Therapie benutzt wurde [4, 5]. Die Kombination von regionaler Infusion und Bestrahlung der Gesichtstumoren hat noch keinen besseren Effekt gezeigt als jede dieser beiden Methoden fuer sich, obwohl die Beobachtungszeit nach der Behandlung dieser Gruppe von Patienten gegenwaertig relativ kurz ist.

Es werden jetzt Forschungen eingestellt, um eine direktere Angriffsmethode der neoplastichen Zellen zu erhalten, indem man eine Kombination benutzt einerseits regionaler Gefaessisolierungstechniken und tumorstroma-spezifischen oder tumorparenchyma-spezifischen (Antikoerpern) therapeutischer Agenten.

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Stereotaxic Apparatus for Operations on the Human Brain

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INTRODUCTION

The apparatus described here was designed by one of us (B. B.) at the suggestion of the other author (H. C. V.). It was put into clinical use in its original form in 1957 and has been progressively modified to its present form. While the original design was an independent one (its similarity to the apparatus of Riechert and Mundinger [1955] was coincidental) we have drawn freely on many other workers in this field during the successive modifications of our instrument. We are especially indebted to Dr. George Manning (1960) for suggestions regarding an x-ray alignment frame, the calculations and plotting of the target and the construction of the phantom target. Spiegel, Wycis, Marks and Lee (1947) described the first stereotaxic apparatus for operations on the human brain. In 1952 Spiegel and Wycis referred to 14 published modifications of their apparatus. A decade later (1962) they add 25 more published descriptions of stereotaxic equipment. Doubtless other useful stereoencephatomes have been devised but remain unpublished.

Objective of Instrument Design

This apparatus has been designed to fulfill as nearly as possible the four objectives of optimum accuracy, versatility without restriction of target area or burr hole position, simple procedural system, and instrumentation within practical cost limits but with the accuracy required for investigative studies.

The principal sources of error encountered in stereotactic work can be classified as follows:

1. Uncorrected x-ray distortion due to x-ray beam out of parallel to the axis of the instrument or anatomical reference planes.
2. Failure to exactly re-position the instrument on the head with successive applications.
3. Errors in visualization of internal landmarks.
4. Inaccuracies in calculations of data or in setting the instrument.
5. Accidental movement or mechanical strain movement of the instrument after setting.

Description of the Apparatus

The apparatus consists of four basic elements exclusive of x-ray equipment as follows:

1. Subframe (Fig. 1A) with guide bushings for holding support pins. This frame carries ear plug and nose bridge attachments for holding the instrument during preparation of skull for socket screws and for their placement. The ear and nose pieces are removed after the frame is attached by means of the pins and socket screws.

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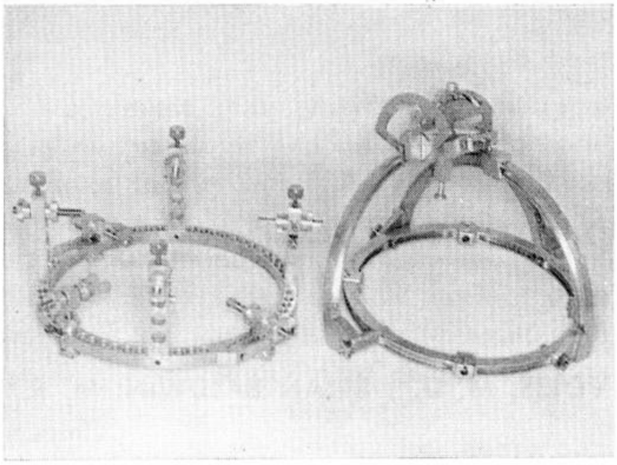

Fig. 1. — *A. Subframe. B. Instrument.*

2. The instrument itself (Fig. 1B) attaches to the subframe and carries the probe guide member. The guide is in the form of a long bushing with the lower bushing extendable down to the burr hole for the maximum possible support. The instrument is set with angular readings taken from the protractors after the phantom set up. All movements are angular. The collet guide section is pivoted for movement with a locus defining a cone with its apex at the surface of a spherical locus. The collet guide section is carried on a semicircular ring pivoted from one axis of the base ring. This section slides to any position along the semicircular ring. This motion along with the pivoting of the large ring creates a spherical locus so that the guide bushing center of rotation may be moved to any position over the head without greatly changing its distance from the skull.

The instrument carries a second large ring which is used as a support to keep the main ring in an accurate position after it is set. The large rings carry angular graduations for recording position and the pivot axes of the guide collet carry pointers which move on protractors mounted at right angles to each other. The four angular readings fully define the instrument setting except that the probe length or penetration depth relative to the instrument is measured independently with a rule or other length gage. The depth is set with an adjustable stop collar attached to the probe.

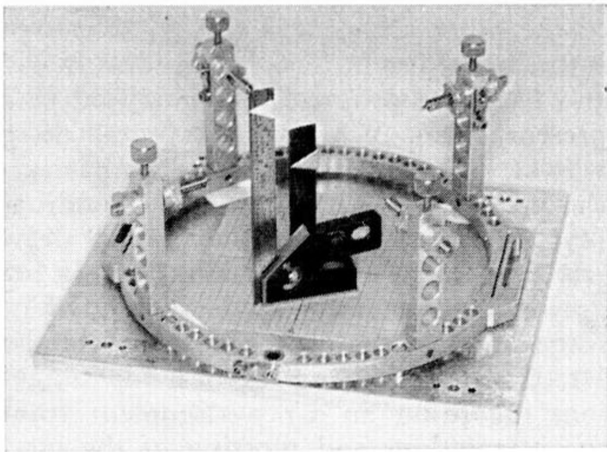

Fig. — 3. — *Mounting plate with upright markers indicating phantom target and burr hole.*

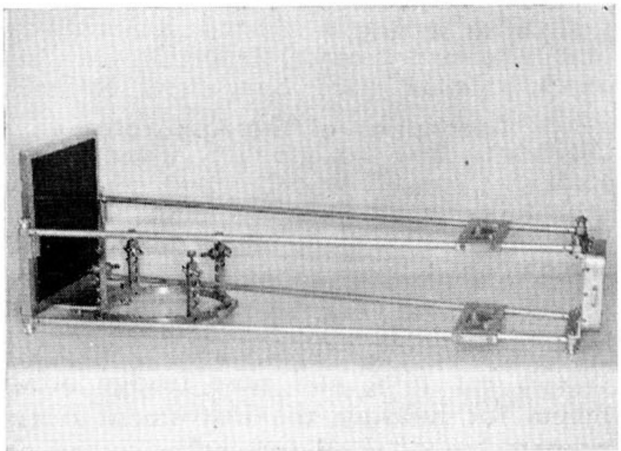

Fig. 2. — *X-ray alignment frame 100 cm. in length shown attached to subframe.*

3. X-ray alignment frame (Fig. 2) is 100 cm in length and is attached to the subframe and to the x-ray tube housing. The frame carries a cassette holder and provides accurate alignment of x-ray source, head and film.

4. Mounting plate (Fig. 3) for holding complete instrument during set up of phantom burr hole and target for setting instrument. The system uses two small uprights with height markers for use as the phantom burr hole and target. Since the instrument is set by the use of a phantom (Fig. 4) the polar coordinates of the instrument are used as a record only. The phantom permits the use of rectangular coordinates for locations of the target.

All parts are constructed of 2024 alloy of aluminum with the exception of small parts of 300 series stainless steel. The total weight of the instrument and frame is four pounds, and of the x-ray alignment frame six pounds. In use the weight of the x-ray alignment frame is partly supported by the x-ray apparatus.

Use of Apparatus

The use of the apparatus requires two sessions in the operating room. General anesthesia may be the first stage if desired,

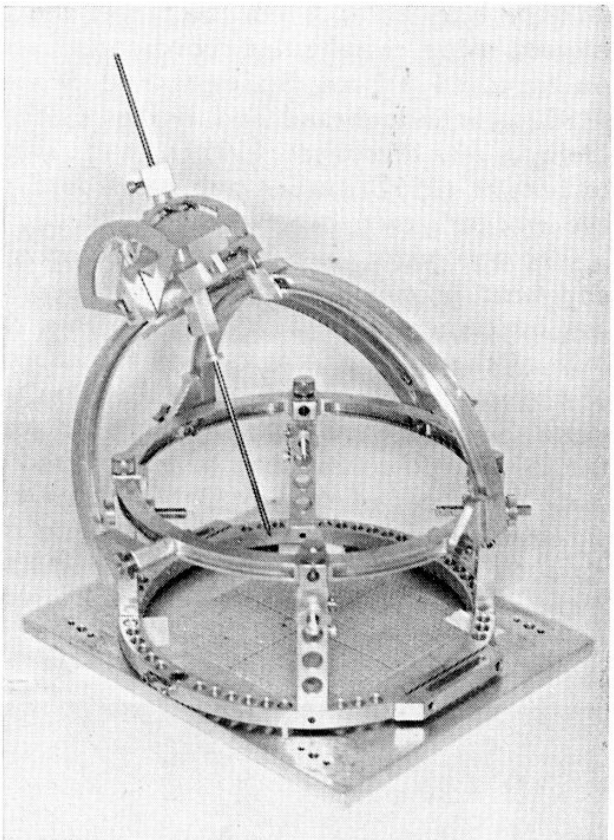

Fig. 4. — Instrument attached to subframe and in turn to mounting plate. The setting of the probe to the phantom target is illustrated.

local is considered essential for the second stage. The first stage is carried out with the patient in the sitting position. The subframe is initially fixed to the patient's head by the earplugs and nasal bridge. These are adjusted so that the earplugs are at an equal depth and diametrically opposite

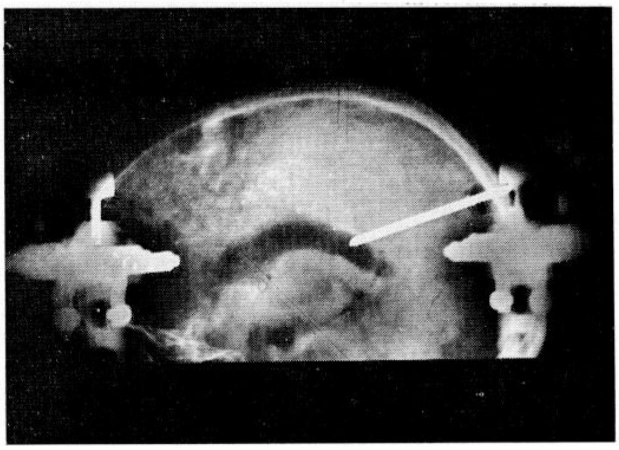

Fig. 5. — Lateral view of the ventriculogram with the subframe attached to the skull. A ventricular cannula has been introduced through a posterior burr hole. The anterior commissure and the posterior margin of the foramen of Monro have been accentuated.

each other, and the base of the sub-frame is parallel to Reid's base line. Stab incisions are made in the scalp opposite the pin bushings in the four posts of the sub-frame. A special Nº 1 drill is put through each bushing in turn and a hole drilled in the outer table of the skull. Now four self-tapping socket screws are placed in these holes, using a special screw driver inserted through the guide bushings. These screws are left in place between the two stages and may remain permanently if desired. Four pins that fit into the sockets of the screws are now inserted through the guide

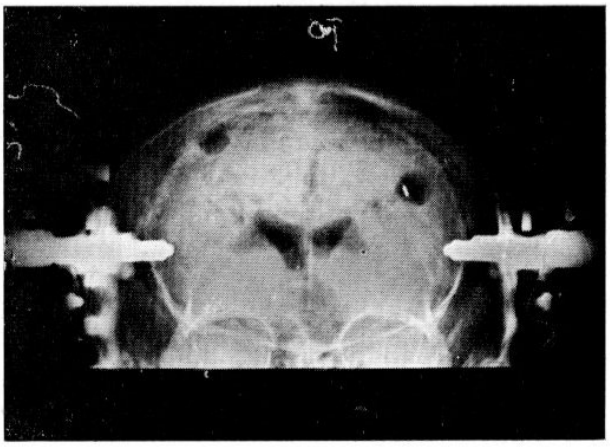

Fig. 6. — Postero-anterior view of ventriculogram with subframe attached to skull.

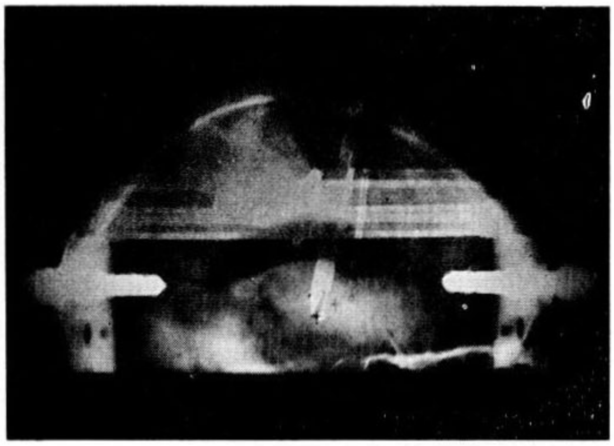

Fig. 7. — *Three lateral roentgenograms of the same case have been superposed. The ventriculogram shows the outline of the lateral ventricle and the foramen of Monro. The anterior commissure is accentuated and two separate targets have been plotted with a small cross. The roentgenogram of the phantom shows the heavy probe directed to one of the targets. The roentgenogram taken at the time of operation shows the ball electrode directed to the same target. The probe and electrode very nearly, but not precisely coincide. The pins for fixation of the localization frame do precisely coincide, showing how accurate superposition of the films is possible.*

bushings and adjusted to as nearly equidistant readings as possible.

Now the ear plugs and nasal bridge are removed as adequate skeletal fixation has been attained. A burr hole is made for injection of air. This may be located for the later stereotactic procedure and if a bilateral procedure is contemplated both burr holes can be made at this time. The x-ray alignment frame is attached to the apparatus and to the tube of an x-ray machine. The initial attachment is for a lateral film. The ventricle is tapped and 15-20 cc. of air are injected without removal of fluid. An x-ray is made and developed. Usually satisfactory visualization of the third ventricle will be obtained (Fig. 5). If not, the head may be manipulated and if necessary, another 5-10 cc. of air shifted so as to obtain a postero-anterior view (Fig. 6). This concludes the first session. The sub-frame is removed, leaving the screws in place in the skull and the scalp incisions sutured.

The calculation procedure follows. The x-rays are studied and internal landmarks (foramen of Monroe and anterior and posterior commissures) identified. The socket screw positions, the internal landmarks and burr hole positions are transferred to special graph paper. This permits a rapid construction of the projected top view of a conventional three plane mechanical drawing. Since the distance of the film from the geometric center of the instrument is known (18.7 cm.) as well as the distance of the tube from the film it is possible to diagramatically show the intersecting rays and plot the true position of the internal landmarks (usually anterior commissure) and the burr holes. Then the target can be plotted using rectangular coordinates based on standard atlases, Spiegel and Wycis (1952), Schaltenbrand and Bailey (1959), Delmas and Pertuiset (1959), and Talairach et al (1957), other published data, or the worker's own experience.

The top view with the plotted target and burr hole is now accurately taped on the instrument mounting plate so that the axes of the drawing correspond to the axes of the instrument which are scribed on the plate. The original drawing may be used for this purpose or it may be transferred to a second sheet of tracing paper. Now the sub-frame and instrument are placed on the mounting plate. The center of the instrument is at a fixed (and easily measured) height above the mounting plate.

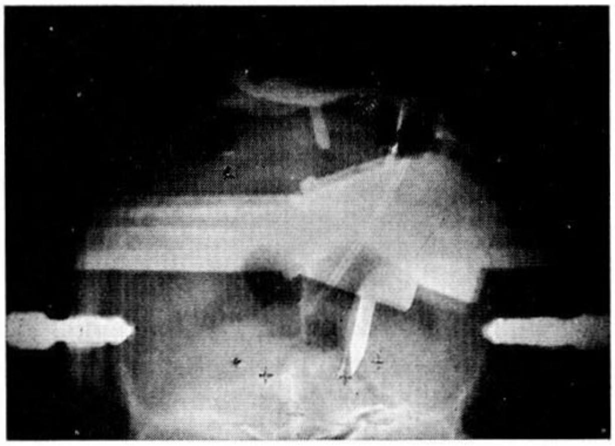

Fig. 8. — *Superposition of the postero-anterior roentgenogram of the same case as Fig. 7. This is not the case shown in Figs. 5 and 6.*

The phantom target and burr hole are located by height markers placed on two uprights placed at the respective points indicated on the top view drawing (Fig 3). The location of the height markers is established from the lateral and posterior-anterior drawings with the necessary correction for the height of the center of the instrument above the mounting plate.

The instrument is now set by maneuvering the probe until it passes through the center of the burr hole to the center of the target (Fig. 4). The instrument is then locked in position. If the x-ray alignment frame is now attached to the sub-frame and the upright markers removed, lateral and posterior-anterior x-rays can be taken and the position of the probe checked superposing these films on the original x-rays or on the drawing constructed from them (Fig. 6 and 7). The length of the probe is recorded as are the readings on the 4-plane protractors of the instrument. This permits resetting of the instrument if the settings become changed before its use.

The actual stereotactic procedure (second operating room session) can be done whenever desired (usually in our practice three to seven days after the first stage). It is carried out under local anesthesia. The previous incisions are re-opened and the sub-frame attached to the skull, seating the support pins in the socket screws in the skull. The instrument is attached to the sub-frame and a special (25 cm. length) Cooper cannula, a needle or a suitable electrode is now marked for depth using the previously recorded depth of the probe marker. It is inserted through the burr hole to the target. The x-ray alignment frame is replaced and lateral and posterior-anterior films taken. The position of the cannula, electrode, or needle can now be checked by superposing these films on (a) the original films (b) the films of the phantom set-up or (c) the drawings made from the original films (Figs. 7 and 8). They should, of course, all correspond if procedure and calculations have been performed accurately. Physiological checks in the shape of procaine injections, inflation of the balloon of the Cooper cannula, or electrical stimulation should, of course, be carried out before a destructive lesion is actually made.

Although further refinements are planned, this apparatus is currently considered to adequately meet the objectives stated at the beginning of this paper.

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Personality

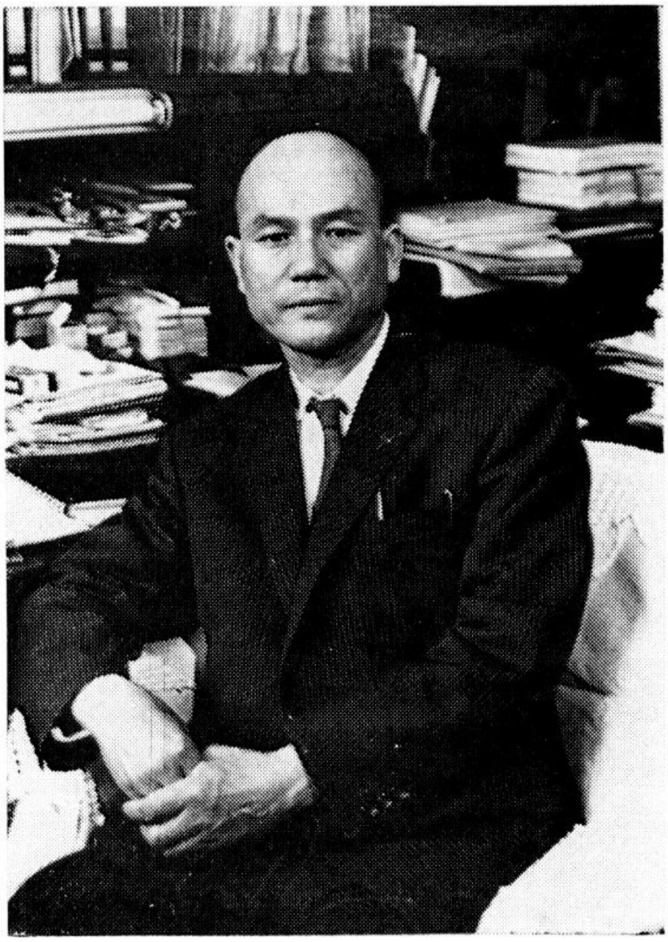
Prof. Dr. SHIGEO OKINAKA

We want in this article to pay homage through the person of Prof. Okinaka to the people and country of Japan.

Every citizen is but a prism through which the historical background, geographical conditions and cultural environment of his homeland are transmitted.

A country has both an apparent and a hidden physiognomy. Fused together Man and Nature build the cities. Will, plus power, plus stones. Intelligence mixed with steel, sand and granite.

If one wants to visit this kind, bald-headed Professor, beloved by his numerous disciples, with his serene, austere expression resembling a Zen monk, one must go to Tokyo where he held the post of Professor of Internal Medecine.



At one's arrival at the most populous city in the world, one feels at first thrilled and baffled by its variety. Tokyo is a burst of never-ending activity, a city under the spell of progress. Technically equal to the finest cities in Europe, it resembles them in some respects until you find certain spots that remind you that this is Japan.

In countries, like people, some qualities are acquired and others inherent in their intimate nature. It is in the realm of subconsciousness that the true traits of their personalities must be found.

Tokyo is just the modern facade of Japan, a supermetropolis crowded with ten and a half million people and crazy traffic, which has charmed and puzzled visitors by its contradictory spirit.

At the Tokyo Imperial University School of Medicine, Prof. Okinaka graduated in 1928 and held the rank of Professor of Internal Medicine; after a brilliant career, he is respected as a scholar of the highest class.

Tall, keen-eyed, with a square, determined jaw, his person inspires a sense of energy, honesty and straightforwardness.

His gifted insight inspires him to discover hidden talents in the young doctors around him. It is the same kind of insight that made Magendie recognize in Claude Bernard, a dull student about to give up Medicine, a great intellectual potential, and to inspire the best of him. It is not by chance that Dr. Okinaka's Department of Internal Medicine is famous for providing many Professors for the University Medical Schools.

He is cheerful and modest, his sincerity and friendliness has won his collaborators respect; good will and harmony always reign in the running of his Service. The flood of papers that are turned out from the different groups of studies under his direction speaks eloquently for its scientific activity. Dr. Okinaka is a hard worker and very inspiring to his collaborators. At 7 a. m. he is already at work.

And it is not rare that he stays overnight at the University when engaged on some scientific problem.

There is in Japan a charming legend according to which Izanagi the Creative Deity, stood on the Floating Bridge of Heaven with a jeweled spear used for stirring the brine thrust it into the ocean, and with the drippings from its tip created the Japanese islands. They are a beautiful present to nature whose contour is said to have been compared to a dragonfly by the Emperor Jimmu. This is the homeland of nearly 100 millions people crowded in a beautiful but not bountiful soil. Only 16% is arable, and the people depend much on the sea for nourishment. A chain of Mountains is the backbone of the main island and 800 ports testify to the maritime traditions of the Japanese people. It is said that there is not a place in the whole country further than 100 miles from the shore.

Majestic snow-capped, peerless Mount Fuji-No Yama, the dominating symbol of Japanese life, is regarded as an emblem of purity and beauty.

Many painters have used it as a central theme of their pictures. The tradition is that Fuji-No Yama rose in one night 2000 years ago. Regardless of the angle from where it is seen, the mountain is always beautiful.

This is a land of great beauty, but Japan also demands of her sons great endurance and resourcefulness. Boiling under the sea are submarine volcanoes that cause almost one earthquake a day somewhere in the country, even though they are only detected by the aid of a seismograph.

Geographically this is the physical setting, the scenery to which Dr. Okinaka opened his eyes in life one October day in 1902, in Kanazawa, a city considered one of the centers of culture, art and gracious living. He was the seventh child of eleven children born to the family of an army officer. His birth preceeded the outbreak of the Russian-Japanese war, by two years. Being a military man, his father was continuously moving from one part of the country to another and so young Shigeo spent his childhood in different cities: Kanazawa, Hamada, Himeji, Hiroshima, Okayama, and Tokyo.

He has no recollections of the Russian-Japanese war which ended when he was just three years old. He considers it a great fortune that his father who had served in the War came back safely home, in spite of the fact that a bullet hit his chest and destroyed a large pocked watch. Years after that event his father used to show his children the remnant of the watch and told them the story of it.

Certainly this was a watch that watched his life!

This episode deeply impressed the boy, and he sensed instinctively, that there was something fatalistic about destiny, and loaded with omens squared his shoulders to life.

Years passed by, kindergarten and primary school were spent in Hiroshima, Okayama and Tokyo. Then by family consensus it was decided that Shigeo ought to follow his father's footsteps and enter for a military career, partly due to the tight financial situation upon his father's retirement from the services.

His intuition about the all-powerful fate proved to be true, and it took the form of a remote relative, a practising doctor who suggested to his parents that he should adopt him. They consented.

Thus the prospective soldier was turned into a medical student, and changed his family name to the present one.

His foster father had a good financial position and practised medicine in the outskirts of Himeji City, Hyogo Prefecture, in a half agricultural and half fishing village.

Young Okinaka completed his middle schooling at Yokohama, and upon finishing the 5 years course, went to the First High School in Tokyo for a pre-medical course.

Dr. Okinaka says, "It was destiny which has led me to the medical career more than my own wish or decision". Pursuing the course of medical education gave him a more profound and lasting joy and satisfaction.

Finishing the four years course in 1928 Dr. Okinaka was ready to go into practice, (there was no internship system at that time). It was his aim to help his foster father in his practice and with that in mind he started his training in Internal Medicine without giving it too much thought.

There were three Departments of Internal Medicine, headed by Prof. Ken Kuré, Prof. R. Inada, who discovered the causative agent of Weil's disease and Prof. Shimazono who was famous for his investigations on Beriberi. Dr. Okinaka chose Prof. Ken Kuré who was interested primarily in the autonomic nervous system and cardiology. He cannot ascertain why he chose the youngest of the three Professors. He believes that it was the fact that he liked the way he taught the students.

Prof. Ken Kuré became for him a symbol of what is desirable in a medical man. He had spent two years in Germany studying the pathophysiology of the heart under Prof. H. E. Hering. At his return he was appointed Professor of Medicine in the University of Kiushu ("Where the Lands End"), in Fukuoka City in the Western part of Japan.

After that he was appointed to the University of Tokyo and it was at that time that Dr. Okinaka joined his Department. Studies were carried on heart diseases, on progressive muscular distrophy and research on the spinal parasympathetic efferent fibers in the dorsal root.

Dr. Okinaka was deeply impressed by Prof. Kuré's personality and has said of him, "He was indeed a physician and research worker of exceptional caliber, devoting himself equally to his research work and the care of the patients. He was always abundant in original ideas and filled with zeal and fighting spirit against the unsolved problems confronting him. I was deeply influenced by his pure, scholarly attitude and endless passion towards science.

Setting aside my plans of becoming a medical practitioner I dedicated my passion and effort to follow his steps in various research projects".

Dr. Okinaka was delighted when Prof. Kuré asked him to accompany him to the First International Congress of Neurology to be held in Switzerland in 1931. It was quite a journey, and for young doctor Okinaka it was his first trip away from his homeland.

They crossed the Pacific by ship and the North American Continent by train, arriving at New York. After crossing the Atlantic they reached the European Continent via England.

They remained for several months in Berlin and arrived at Bern, Switzerland on September to attend the First International Congress of Neurology. This trip made Dr. Okinaka become deeply interested in Neurology. Almost every leading scientist in Neurology from all over the world was gathered there.

There he met Dr. S. W. Ranson of Chicago, Dr. C. S. Sherrington of Oxford, Dr. H. H. Dale of London, Dr. E. D. Schaefer of Edinburgh; Dr. L. R. Müller of Erlangen, Dr. O. Foerster of Breslau, Drs. C. and O. Vogt, Dr. M. Bielschowsky of Berlin-Buch.

He also recalled the presence of Drs. Pavlov, Cushing, B. Sachs, Economo, Marburg, Westphal and Robert Bing, among others. This embraces almost all the most famous Neurologists in fundamental and clinical science at that time and those who have played a great role in the development of modern Neurology.

Besides during this trip he had occasion to contact personalities in different fields of Medicine such us Dr. E. Landsteiner (New York), Dr. A. V. Hill (London), Dr. Jacobaeus, Dr. Howgren, Dr. Euler, Dr. Liliestrand of Stockholm, Dr. Boeke of Utrecht, Dr. Crogh of Copenhagen, Dr. H. E. Hering of Köln, Dr. Mollendorg and Dr. Aschoff of Freiburg, Dr. Volhardt of Frankfurt, Dr. C. V. Bergmann of Berlin, Dr. Morawitz of Leipzig, etc.

He came back to Japan greatly inspired bringing with him a deep and unforgettable impression, having witnessed the discussions among the best minds in Neurology and talked with many distinguished Nobel Prize Winners. He continued his work with Dr. Kuré with whom he turned out many scientific papers.

Meanwhile, his foster father was patiently waiting for him to finish his training in Internal Medicine and join him in his practice. But Dr. Okinaka gradually lost his interest in practicing Medicine, and this change seems to have been so natural, that no one around him was surprised.

In 1938 his foster father died and in 1940 Prof. Ken Kuré, also died suddenly from a myocardial infarction.

These were two severe blows for Dr. Okinaka and deeply saddened him. By that time Dr. Okinaka was regarded as an independent research worker and an internist in medical circles. But he had already laid his plans for the future, and took decisive steps, giving up medical practice to dedicate all his effort to his academic career.

Then, the Second World War broke out, and Dr. Okinaka states that it was as destructive in his life as in the whole country itself. But he never abandoned his research work, even though many of his colleagues were drafted, he continued his scientific activities working with a small group in semi-darkness, with their helmets on prepared for eventual air raid attacks. In 1943 he was promoted from Lecturer to Assistant Professor and finally to Professor of Medicine, of the University of Tokyo Faculty of Medicine in 1946.

For the next fifteen years Prof. Okinaka was actively engaged in rebuilding each field of Internal Medicine which had suffered a considerable setback from the war.

Several groups were formed, each of them dedicated to some special branch of Medicine, Neurology, Cardiology, Endocrinology, Haematology, Gastroenterology,and Pulmonary Diseases. The enthusiastic cooperation of the young doctors who were members of his staff in this endeavor proved to be very effective in carrying out Dr. Okinaka's plans in Clinical, educational and research fields.

Neurology was in those days not organized as an independent Department, But Dr. Okinaka gave it great impetus and a powerful group from this discipline was formed with distinguished Neurologists.

Dr. Okinaka believes that the progress of Neurology mostly depends upon the participation of internists.

The Department of Internal Medicine of Kyushu University headed by Prof. Katsuki is functioning on the same lines. Many of the Neurologists in both services have studied in famous centers in the United States and are well equipped to be the future leaders of Neurology in Japan.

Recently one of them, Dr. Kuroiwa was appointed Professor of Neurology, thus establishing for the first time an independent Department of Neurology. Dr. Okinaka founded the First Neurological Society of Japan, and it met regularly every year.

The World Federation of Neurology and the National Institute of Health have been enthusiastic supporters of these efforts toward the growing development of Neurology in Japan.

Not only outsiders have been eager to encourage this movement, but also several Departments of Internal Medicine in Japan have helped. Dr. Okinaka recalls with gratitude the efforts of Prof. Dr. S. Katsuma of Nagoya University, a member of Japanese Academy of Medicine, who has always provided helpful and thoughtful suggestions.

Dr. Okinaka has achieved a well rounded life. His activities as a leader have flourished in a generation of outstanding doctors, who talk about him with deep gratitude and admiration. The same that Dr. Okinaka has had for Professor Kuré.

Gratitude is a wonderful trait of the Japanese personality, it is always present in their appreciations for the benefits received.

As to his personal achievements Dr. Okinaka was given one of the greatest distinctions open to a medical man in Japan. He was awarded in 1961 the Imperial Prize of the Japanese Academy for his outstanding work on the autonomic system.

Dr. Okinaka has carried on important research and clinical work on the following neurological topics.

1) Clinicopathological Studies on Cerebro-Vascular Disorders.

2) Clinicopathological Studies on Atherosclerosis (Brain and Heart).

3) Hepatocerebral Disease.

4) Survey of Multiple Sclerosis and Allied Disease in Japan.

5) Studies on the Autonomic Nervous System.

Professor Okinaka has made important contributions to medical literature and among these are a "Text Book of Internal Medicine" edited by him, one of the best of its kind, a book on Autonomic System by Dr. Kuré and himself. It has become a classic and a source of inspiration for workers on this field.

He has also written a book on Cerebrovascular Diseases with the collaboration of Drs. Kuroiwa and Tzubaki which is a widely known in Japan and embraces clinical and pathological studies.

Dr. Okinaka's opinion is highly respected and there is in circulation an annecdote that tells how on one occasion he was consulted about the physical condition of a Prime Minister. In spite of the fact that there were important political interests at stake, Dr. Okinaka's opinion after medical examination resulted in the Prime Minister's resignation. It was a remarkable story and everybody commented how a single doctor's opinion changed the political panorama in Japan.

Some time ago, when in a letter-interview, we asked him about his family life, Dr. Okinaka stated "As to my personal history, I entered my family life without a romance to talk of, because it was arranged for me to marry my present wife, when I was adopted". This was customary in Japan where the elders used to protect, in this way, the future happiness of their children.

"My wife 'he continued', is healthy and happy, but to our great regret a junior has not been born to date. Since my wife has never accompanied my trips abroad, it is my hope to take her with me one of these years".

Dr. Okinaka has retired recently from his Chair of Internal Medicine but still remains as a creative force working and encouraging others to excel in their endeavours.

The crop of goodness has been plentiful and Dr. Okinaka remarks "I am looking back over these years of my life with profound gratitude and satisfaction".

"I have personally educated almost a hundred physicians as internists, many of whom are provided with outstanding abilities. It will be not only a great hope and pleasure but also a worth while job to help and observe the future growth of these pupils as leading physicians and investigators".

This is the brief account about the life of Prof. Okinaka one of the most brilliant minds of Japan, and man of good will, modesty and courage.

East and West are merged in Japanese contemporary culture in a delicate balance. It has been claimed that Japan is the most Westernized country of Asia.

But is also true that they have a queer way that is almost an instinct in choosing what was needed to progress without doing violence to their own traditions. And we are thankful for it. There are many aspects from which Westerners may benefit by observing their way of life.

Japanese courtesy, is a magnificent trait of their character. That has made possible the miracle of an orderly life in a crowded country. In business this means fair play. In science, mutual respect and thankfulness to their teachers. In every Japanese person there is something of Tokyo, an open mind to other ways of thinking, living and doing and something of Kyoto, which is not only the reverse of Tokyo in its reading but also in its meaning. Tokyo is but a modern glowing facade and in a way a materialistic view of Japan.

Kyoto whose meaning is "Peace and tranquility" shows us the inner spirit of Japan and the secret of its charm.

Resting at the foot of an attractive semi-circle of hills, Kyoto is medieval Japan living side by side with the modern one, with its alluring beauty.

We remember our impression when Dr. Araki, Professor of Neurosurgery in Kyoto and Dr. Tada took us on a tour of its magnificent gardens.

In entering the Garden of the Saihoji Temple we were so bewitched by its beauty that we could hardly utter a word. Dr. Araki stood near us comprehensively smiling and gazing at our admiration through his glasses.

For 600 hundred years this place has astonished its visitors. It is a velvet garden carpeted by seventy hues of different kinds of moss. Murmuring water leads the visitors to the tea house, where the Zen Monks used to sip tea to keep awake during the long hours of meditation.

Another garden, striking for its abstract beauty, the Sand garden, five centuries old, has a serene simplicity that reflects the ascetic life dedicated to unveil truth through perceptive thinking. It is comprised of 15 large rocks striking austerely out of raked sand.

There are others like the famous tea garden of the Katsura Imperial Palace that show us why art is so embedded in Japanese daily life.

Landscape gardening is a true homage of art to nature, making her more endearing to her children.

The most exact feeling trusted to our hearts was one of reverence, and we seemed to regain a sense of belonging, of coming back to a home, that was once a universal one to makind: Nature.

There is in the hidden core of every country a piece of trascendental reality that is mirrored through its customs, way of living and symbols.

Wholeness of human personality is only attained when the spiritual doors are opened to give and to receive the best in the human interchange being, art science or style of life.

Dr. VICTOR SORIANO.