ROENTGEN THERAPY AND CYCLOPROPANE SENSITIVITY

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THE following case is reported since there is little reference in the literature to unusual responses under anesthesia following radiotherapy. These findings may also be of significance during the treatment of casualties following an atomic explosion.

The patient was a 39 year old man who had had a course of deep roentgen therapy to a carcinoma of the floor of the mouth. The therapy had been completed five weeks before operation was scheduled. He was in good general condition, had not lost a significant amount of weight, and had been able to eat normally since there had been no radiation sickness. The left lower face was extremely sensitive to touch from the midline of the chin to behind the angle of the jaw. This area of hyperesthesia coexisted with complete epilation of the beard. A two stage operation was planned in which suitable skin pedicle grafts would first be fashioned for use at the second stage when reconstruction of the lower jaw was to be carried out after resection of part of the mandible.

Premedication was 100 mg. of pentobarbital by mouth one and one-half hours preoperatively, followed by 10 mg. of Pantopon® and 0.4 mg. of scopolamine given subcutaneously an hour before the operation. Induction of anesthesia was with thiamylal sodium intravenously in divided doses up to 500 mg., and when the patient was apparently stabilised on cyclopropane with 10 ml. of ether in closed circuit with oxygen, he was given 40 mg. of succinylcholine chloride for intubation. Following this manoeuvre, he was gray and pulseless, but only briefly, since the peripheral circulation returned after the lungs had been inflated with oxygen; it was presumed that this was a brief episode of ventricular standstill by vagal inhibition.

It proved virtually impossible to maintain this patient on cyclopropane because of the extreme and unusual sensitivity that he showed. After a flow of this gas of 200 ml. per min. had been allowed to enter the closed circuit for 2 to 3 minutes, respiratory arrest followed which lasted for approximately half an hour. The patient responded to painful stimuli before respirations became properly reestablished. This sequence was repeated several times using smaller additions of cyclopropane, but a plane of surgical anesthesia was impossible to ob-

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tain without having complete respiratory arrest. Pulse and blood pressure, however, were relatively unaffected. Eventually, the use of cyclopropane was discontinued, and nitrous oxide with minimal ether, and Demerol® intravenously was substituted. He did not prove unduly sensitive to this combination, tolerating amounts that experience suggested was normal for a person of his age and sex. Recovery was uneventful following the surgery which took five and one-half hours, and there seemed to be no reason to believe that the brief circulatory collapse during intubation could have produced a significant degree of cerebral hypoxia.

The second stage of the operation was undertaken a month later. A tracheotomy was first carried out to establish an airway that would not hamper reconstruction of the mouth. Anesthesia with cyclopropane was avoided. Instead, thiopental sodium, nitrous oxide, Demerol and Nisentil® were used. The patient's tolerance of these last two respiratory depressants seemed, if anything, to be greater than usual. After a procedure lasting almost eight hours, postoperative recovery was uneventful.

Discussion

An extreme sensitivity to cyclopropane may be shown by elderly people, especially if their premedication has included a respiratory depressant such as morphine, but the same is not usually seen in younger adults. The selective depression of respiration with poor analgesia during maintenance is even more uncommon. Significance is given to this isolated case because of the observation of Wilson (1) that animals exposed to roentgenization of the whole body showed an especially poor tolerance for cyclopropane, but not for ether, ethylene, nitrous oxide, or thiopental sodium. In his account it appeared that death under cyclopropane anesthesia resulted from respiratory failure occurring at an abnormally light plane.

Normal radiation therapy would probably not have such an effect on human beings unless the cerebrospinal axis is in the path of the beam. Even then, the central nervous system is unusually resistant to radiation, as has been pointed out by Ross *et al.* (2). Hsu *et al.* (3), who carried out studies on the effect of radiation on the permeability of the blood brain barrier in deteriorated schizophrenics, found a definite increased permeation of substances into the cerebrospinal fluid after epilating doses to the scalp. This is probably because the vascular components of the brain do not show the same resistance as the neurones. Relatively small doses of roentgen rays might so increase the permeability of the pial vessels and the choroid plexus that response to some drugs could be altered or accentuated. Present-day experience suggests that the optimum radiation dose for treatment of oral cancers is in the neighbourhood of 6,000 r., which some radiologists give over a relatively short period, although 3 to 5 weeks is preferred

(4). When the growth lies close to the pharynx or the roentgen ray beam is directed antero-posteriorly it may be impossible to irradiate without involving the brain stem and medulla.

It should be noted that Clemente and Holst (5) found that 1,500 *r.* was sufficient to produce neuronal damage in the brain of monkeys when given as a single dose to the whole head, although there might be no obvious neurological signs of damage in these animals and radiation sickness was conspicuously absent (2). They were noted to be more sensitive to the narcotic effect of pentobarbital.

The brain areas so damaged appear to be remarkably constant (5). The posterior hypothalamus is first affected, followed by the medulla and the rest of the hypothalamus. Clemente and Holst (5) suggest that such specificity of effect may not depend on sensitivity to the direct radiation but may be conditioned by scatter radiation arising from the adjacent bony skull.

Therefore, it seems possible that radiotherapy for neoplasms in the mouth may cause at least minor degrees of damage to the brain stem area from direct or scatter radiation. Such damage might not be permanent; thus any effects seen might be transient.

It is interesting to consider what nervous functions may be disturbed. In the studies on monkeys, damage was especially marked in the brain stem reticular formation, which is essential for the production and maintenance of consciousness (6, 7), and in certain dorsal nuclei of the medulla which may include part of the respiratory centre. The spinal root nucleus of the trigeminal nerve and some of the vagal nuclei were affected.

In the areas of the hypothalamus affected may lie centres responsible for the co-ordination of somatic and autonomic activity into protective reflexes of the respiratory tract—salivation and jaw movement, coughing, laryngospasm, vomiting and movements for the expulsion of foreign bodies (8). These are of especial concern to the anesthesiologist A vagal component is prominent in most of these. Disturbances of temperature regulation were seen in some of the experimental animals that became poikilothermic.

The local hyperesthesia of the face and oropharynx in areas supplied by the trigeminal nerve and vagus could contribute towards abnormal reflexes arising from damage to the brain stem nuclei. While the degree of damage following radiotherapeutic treatment would probably not be sufficient to cause neuronal destruction, it could well lead to degrees of hyperirritability of the involved neurones or nuclei. Involvement of the vagal nuclei would then make cardiac irregularities possible because of excessive vagotonia accentuated by cyclopropane. A vagovagal reflex seems to be a common factor precipitating cardiac arrest (9). Since such hyperirritable cells are more susceptible to depressant drugs, depression of the respiratory centre by cyclopropane seems a possibility. The fact that morphine-like compounds

do not seem to have the same depressive action suggests that they act at a different level, and indeed they do not produce the same pattern of depression as does cyclopropane. Breckenridge and Hoff (10) collected evidence from animal experiments with morphine to suggest that its effect might be at a mid-pontine level rather than in the medullary respiratory centres.

Summary and Conclusions

A case is reported in which excessive respiratory depression with cyclopropane followed radiotherapy for a new growth in the floor of the mouth. Cardiac irregularity following intubation was also noted.

A review of certain animal experiments is thought to offer an explanation for this clinical observation.

It is suggested that irradiation around the head in appropriate doses may increase the permeability of intracranial vessels, thereby allowing entry to certain drugs (for example, relaxants) that are normally excluded by the blood brain barrier. Drugs which normally penetrate may do so in greater degree. The peculiar pattern of neuronal radiation damage seen suggests that an excessive vagal tone may increase the hazards of intubation with cyclopropane, that consciousness may be more easily depressed, and that disturbances of temperature regulation may be encountered.

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