THE EFFECTS OF INTRACAROTID DIODRAST*  

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The increasing popularity of Diodrast angiography since 1938 has been motivated by the obvious clinical value of this procedure, but it is surprising that no investigations of the action of Diodrast on cerebral function have been undertaken until recently. The occurrence of complications following cerebral angiography has been poorly documented in the past and, indeed, has often gone unrecognized. However, the recent widespread enthusiasm for angiography has resulted in an increasing awareness of the clinical sequelae of this procedure. Physiological investigation into the causes of these sequelae has been almost totally lacking. For these reasons, it seemed pertinent to study the effects of intracarotid Diodrast.

METHODS

Experiments were carried out in 12 monkeys (Macacus rhesus), 4 cats, and 10 humans. Of the 12 monkeys, 6 were anesthetized with Dial,‡ 1 with pentobarbital, and in the remaining 5 the surgical exposure was carried out under pentothal anesthesia with the experimental recording being done under local anesthesia in the neck. One of these monkeys was paralyzed with dihydro-beta-erythroidine hydrobromide.§ All of the cats were anesthetized with Dial.‡ In the humans the recording was carried out under local anesthesia in 5 cases, with intravenous pentothal in 4, and with vinethene-ether in 1 case.

With the exception of 5 human cases where the Diodrast was introduced by percutaneous puncture of the carotid artery, all carotid injections in the remaining humans and in all the experimental animals were accomplished by means of an inlying polyethylene catheter. In the animals a PE 20 polyethylene catheter was introduced into the surgically exposed common carotid artery and usually threaded up the internal carotid artery to the base of the skull. In humans a PE 50 catheter was used in the same manner.

The electroencephalograms were recorded on 8-channel Grass or Offner instruments using small needle electrodes inserted into the scalp. Bipolar recording was used throughout, and the electrode placements were the same in all cases. The arm-to-arm electrocardiogram was likewise recorded on the EEG. Continuous recording of the cerebrospinal fluid pressure was carried out in animals by means of a  

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nylon catheter ligated in the lower end of the dural sac after the tip of the catheter
had been threaded up to the mid-thoracic level. This catheter was directly connected
to a Statham strain gage whose output was recorded by a carrier-wave amplifier
and ink writer.

Changes in the caliber of pial vessels were observed in certain animals after wide
bilateral exposure of the cerebral hemispheres, by a modified Forbes window inserted
into a small trephine hole, and by a lucite calvarium. In the latter instance the entire
bone calvarium of a monkey was aseptically removed. An acrylic plate, molded
to the removed calvarium, was inserted in position by multiple wires. In addition to
visual inspection, high speed color motion pictures were taken of the pial circulation
during Diodrast injection.

Thirty-five per cent and 70 per cent Diodrast solutions were both used in each
case except in two humans where only 35 per cent solutions were used. The order
and timing of the injections of the different strength solutions were so arranged that
the effects observed were clearly a direct result of the immediately preceding in-
jection. The temperature of the injected Diodrast was maintained by a controlled
temperature water bath. Cool solutions were maintained at 70°F., and warm solu-
tions at 99.8°F. The injection time was kept constant for each case. The volume of
Diodrast per injection was 2½ cc. for cats, 4 cc. for monkeys, and 10 cc. for humans.
Adequate precautions were taken to maintain sterility and to guard the Diodrast
solutions against light. Stellate blocks, when performed, were carried out with 1
per cent monocaïne, using minimum volumes to obtain maximal homolateral pul-
py constriction.

RESULTS

The effects of intracarotid Diodrast on the brain seem to be twofold. First, a direct vascular effect and, secondly, a neuronal or cellular effect. The vascular effect is a short, severe vascular spasm followed by a longer
lasting vascular dilatation. The neuronal effect may be a result of direct
toxic action of the drug on the brain, or possibly a combination of this and the vascular changes.

Vascular Effects. The cerebral vascular effects were studied by direct
visualization of the cortex during the Diodrast injections and also by con-
tinuous measurements of the intracranial pressure during and following Dio-
 Trout injections. Direct cortex visualization showed, in all cases, a severe
vasodilatation of the pial arterioles starting at the midpoint of the injection.
This began as a high speed, repetitive series of momentary arteriolar con-
strictions which gave a fluttering appearance lasting only a few seconds. This
was replaced by cortical blanching in which the dark veins stood out in star-
ting contrast. This second phase always began during the end of injection
and lasted for 60 to 90 sec., definitely after the completion of injection. This
was followed by the third phase consisting of a cortical blush lasting 1 to
2 min. Both 35 per cent and 70 per cent Diodrast caused these changes,
though changes induced by the 70 per cent solutions were always more se-
vere. Injection of similar volumes of saline under identical conditions showed
none of these effects.

The results of continuous recording of intracranial pressure changes dur-
ing Diodrast injections showed a constant pattern when room temperature Diodrast was used (Fig. 1A). The rapid initial pressure drop of 10 to 15 mm. of water during the terminal 2 to 3 sec. of injection corresponds to the observed vasoconstriction phase. Presumably this drop is secondary to the rapid and severe initial vasospasm. The rise in pressure immediately following this drop is transient and corresponds temporally to the vasodilation and

cortical blush phases of the observed vascular effect. There was no prolonged effect on the CSF pressure beyond 5 to 6 min. after injection. In this aspect, 35 per cent solutions caused just as marked pressure changes as did the 70 per cent solutions.

To substantiate this correlation between the initial pressure drop and the initial vasospasm CSF pressures were recorded during intracarotid Diodrast injection before and after unilateral stellate block, since stellate block should alter changes that are of vasomotor origin. In all cases the initial pressure drop which was present before the stellate block was completely abolished after the stellate block (Fig. 1B).

Furthermore, since warm and cool solutions should theoretically have different effects on vascular spasm, pressure records during the injection of warm and cool Diodrast were compared. In the same animal there always
was a very definite difference in the pressure response. The cool (70°F.) Diodrast routinely produced twice as much initial fall in pressure as did the warm (99.8°F.) Diodrast (Fig. 1C). Frequently the secondary rise in CSF pressure was significantly greater following the injection of the warm solution than following the cool solutions. The opposite effect was never observed. These changes were never seen after injection of warm or cool saline.

**EEG Effects.** The neuronal effects were studied by electroencephalograms taken during and following the injection of Diodrast. The acute EEG changes have been varied and exceedingly complex to analyze, apparently due to the large number of variables involved. These include the presence or absence of CNS lesions, the depth and type of anesthesia, the strength of the Diodrast solution and the temperature of the injected Diodrast as well as concomitant cardiac and respiratory effects. A statistical analysis of the EEG changes is thus not possible. The effects of 35 per cent and 70 per cent Diodrast solutions differed only in the degree of severity of the reaction. Thus both solution strengths produced similar EEG changes, differing only quantitatively. The observed acute effect on the EEG can be divided into two broad groups, those in which a negative effect occurred, and those in which a positive effect was produced. Negative effect as used here means the reduction in amplitude of rhythmic discharges, or in the case of recurring transients such as spikes, a reduction in either amplitude or frequency. A positive effect denotes the production of new wave forms, increase in amplitude of rhythmic discharges, or in the case of recurrent transients such as spikes, an increase in either amplitude or frequency.

Negative effects on cortical electrical activity were exhibited in two ways: (1) by flattening of all wave forms; and (2) by loss of spikes. Within this category generalized flattening of the EEG was most frequently seen (Fig. 2A). When present, it always started during the terminal half of the Diodrast injection and usually lasted 10 to 20 sec., though a duration of 1 or 2 min. occasionally occurred. The recovery periods were of variable duration and character, though almost all the EEGs returned to the pre-injection pattern within 20 min. When the EEG flattening occurred acutely during unilateral injection, the depression of cortical activity was bilateral, although the flattening was occasionally asymmetric. The EEG flattening involved all wave forms present at the start of injection, and occasionally was so marked that the cortical activity appeared almost isoelectric. In two instances chronic flattening of the EEG occurred and was always on the side of injection (Fig. 2B). In these cases hemiparesis occurred associated with marked flattening of cortical activity on the side of injection. In one animal the paresis cleared and the EEG returned to normal in 3 days. In the other, an epileptic monkey, the paresis cleared in 1 week, although the EEG still showed marked flattening on the side of injection 5 weeks later. Initial loss of cortical spikes occurred following Diodrast injection at least once in all epileptic monkeys (Fig. 3). If the spikes were bilateral the Diodrast injection
Fig. 2. EEG depression. (A) Acute flattening in all leads. (B) Chronic flattening on the side of injection.

Fig. 3. EEG depression. Loss of bilateral spikes.
abolished the spikes on both sides as illustrated. In a lateralized spike focus loss of spikes occurred homolaterally. The loss persisted for 2 to 3 min. after the injection. It is of passing interest that a spike focus was abolished for 3 min. in one epileptic monkey during carotid occlusion for the purpose of closing the puncture wound after a series of Diodrast injections. Occlusion of the carotid artery prior to injection did not have this effect. The positive effects on cortical activity are divided into (1) augmentation of slow wave activity; (2) delayed bursts of spikey 14/sec. waves; (3) generalized increase

in fast activity and spike production; (4) augmentation of spikes; (5) spike and dome activity; and (6) seizure discharges.

Augmentation of delta activity was a constant finding in cases showing slow waves in their control EEGs. This increase in slow wave activity persisted as long as 2 hrs. following injection. When these slow waves were focal, only focal augmentation occurred (Fig. 4A). When generalized delta activity was present, the augmentation was generalized (Fig. 4B). In Fig. 4A a slow wave focus is demonstrated in the right parietal region surrounding an intracerebral angioma. Following angiography a marked increase in the focal delta occurred lasting 30 min. The generalized delta activity present in the EEG of a sick monkey is shown in Fig. 4B, where a marked increase in the generalized slow wave activity occurred after Diodrast injection. It
should be pointed out that this augmentation of slow activity, which by the
definition adopted falls into the class of positive effects, was apparently as-
associated with a functional reduction in activity as judged clinically by im-
pairment or loss of consciousness.

The homolateral production of delayed spikey waves at 14/sec. occurred
frequently and is illustrated in Fig. 5A. These bursts were always on the side

![Fig. 5. EEG activation. (A) Delayed bursts of 14/sec. spikey waves. (B) Focal increase in fast activity, spike production. (C) Augmentation of spike activity.](image)

injected and never appeared before 1 to 2 min. after injection, persisting in-
termittently for 1 to several min. These wave complexes were never seen in
the control EEGs.

Homolateral augmentation of complex fast activity appeared often and
usually started within 30 sec. following Diodrast injection, and lasted from
1 min. up to 1½ hrs. In some instances the augmented fast activity was
quickly replaced by spikes. In others, unilateral spikes alone were produced
immediately following injection with no antecedent fast activity. In epilep-
tic monkeys exhibiting spikes in their pre-injection EEGs, these spikes may
be augmented. It was possible to trigger these spikes by auditory stimuli on
occasion. The human cases with pre-existing temporal lobe spikes or sharp
waves consistently showed some augmentation of these abnormalities. Some
of these changes in the monkey are illustrated in Fig. 5B where homolateral spikes were produced as well as augmentation of complex fast activity in channel 2. In Fig. 5C marked augmentation of pre-existing spikes was produced in an epileptic monkey by injection of Diodrast. These augmented spikes approach a seizure discharge although no seizure occurred.

Spike and dome activity (Fig. 6A) was seen only in monkeys after intracarotid Diodrast. In these cases the injection produced 6 to 10 sec. of generalized flattening followed by a build-up period of complex wave patterns lasting 30 to 60 sec., culminating in a spike and dome discharge as illustrated. In the experiment illustrated the animal was an epileptic monkey in which the cortical spikes had been abolished by a single injection of Diodrast 4 min. prior to this injection.

Seizure discharges were severe when they occurred. It is significant that in two instances clinical seizures took place in the presence of barbiturate anesthesia. The clinical seizures and the seizure discharges in the EEG always occurred almost immediately following the injection, and in only one instance was the seizure lateralized. The electrical recording of such seizures can be demonstrated in its entirety only in animals paralyzed with dihydro-beta-erythroidine hydrobromide, as shown in Fig. 6B.

It is impossible to determine what portion of these changes in neuronal activity is due to the already demonstrated vascular changes and what may be the result of the drug acting directly on the nerve cell. It has been demon-
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...strated that intracarotid Diodrast results in initial vasospasm followed by longer lasting vasodilatation, as judged both by direct visualization of intracranial vessels and by quantitative measurement of intracranial pressure. Furthermore, injection of cool Diodrast causes more vasospasm than warm, and both of these effects are minimized by unilateral stellate ganglion block. On the basis of these observations one might postulate that two effects exist: (1) a direct toxic action on the nerve cell; and (2) a protective vasospasm

...which minimizes the amount of toxic substance reaching the nerve cell in any given period of time. If this were the case, injection of warm solutions, which cause less vasospasm, should produce greater neuronal changes than injection of cool solutions. Likewise, blocking the protective vasospasm should also produce even greater toxic neuronal effects as judged by the EEG.

In Fig. 7 the effects of injection of warm and cool solutions of Diodrast are compared in a human epileptic patient under light pentothal anesthesia. The initial injection of warm 35 per cent Diodrast abolished the pentothal bursts, leaving the abnormal sharp and slow wave activity standing out in contrast. After the EEG had returned to its previous level 5 min. later, an injection of cool 35 per cent Diodrast produced only minimal changes. Thus,
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injection of a warm solution, which produced only minimal protective vasospasm, allowed a greater amount of the drug to reach the nerve cell and produce toxic effects as judged by the EEG changes. The greater vasospasm produced by subsequent injection of the cool solutions protected the nerve cells and minimized these changes. This occurred in spite of a greater toxic action which might be anticipated due to the accumulated dosage. This has been a routine observation in all human and animal experiments when an EEG change was produced. Furthermore, all three of the seizure discharges produced in this series were produced only by warm solutions of Diodrast. Likewise, 90 per cent of all instances of augmentation of delta wave activity were the result of injection of warm solutions of Diodrast. These effects were

![Fig. 8. Increased neuronal depression following stellate block.](image)

never seen after injection of warm and cool solutions of isotonic saline which was carried out in every case.

In Fig. 8 initial injection of warm Diodrast in an awake, epileptic monkey produced minimal flattening of the EEG with abolition of spikes. Thus, injection of the warm solution reduced the protective vasospasm and caused a moderate direct toxic action on the neurones. After the EEG had returned to its previous level 10 min. later, a homolateral stellate block was performed. Reinjection of a warm solution of Diodrast now caused very striking EEG depression lasting 6 min. as illustrated, the spikes being abolished for 2 hrs. The only animals that died acutely following intracarotid Diodrast were two cats on which unilateral stellate blocks had been done prior to the injection. Thus stellate block minimizes the protective vasospasm and allows a greater concentration of dye to reach the tissues where its direct cytotoxic action can be demonstrated. However, it was found in other experiments that even
after homolateral stellate block, injections of warm solutions of Diodrast still caused somewhat greater EEG effects than cool solutions.

**EKG Changes.** Various EKG abnormalities were observed during and following the intracarotid injection of Diodrast. Fig. 9 summarizes some of these. In Fig. 9A there is vagal slowing for a single beat with loss of the “p” wave which occurred during the period of injection. Persistent bradycardia with intermittent loss of “p” waves may also occur as illustrated in Fig. 9B, this effect occasionally lasting as long as 2 min. These two effects were fairly common observations in both the human and monkey. In one monkey rhythmic ventricular extrasystoles occurred (Fig. 9C) over a period of almost 3 min. There is circumstantial evidence that these are the result of central nervous system changes mediated by the vagosympathetic system. The fact that these EKG changes occur more frequently with intracarotid than with intravenous Diodrast would suggest that a direct myocardial action is not the cause. In all instances where no EKG effect was obtained in the present series, the injection was below the carotid bifurcation. This would suggest that these abnormalities are not mediated through the carotid sinus mechanism. It also suggests that these abnormalities are not due to a direct myocardial action, since the dilution factor is the same regardless of the level of injection into the carotid system. All injections through a catheter threaded up to the base of the skull resulted in some type of EKG or pulse rate abnormality, presumably due to the higher concentration of Diodrast reaching the brain.

**Miscellaneous Effects.** The occurrence of seizures, monoparesis and transient hemiparesis has already been described. Apparent reversal of a post-injection hemiplegia was produced by stellate block in one monkey. Homolateral dilatation of the pupil with conjunctival injection and tearing were routinely observed in all animal and human cases. This is doubtless due to Diodrast reaching these structures via the ophthalmic artery. In those instances where the injection was done by needle puncture below the bifur-
cation of the carotid artery in monkeys, swelling and edema of the neck muscles and soft tissues always occurred very shortly after the injection of Diodrast. This effect is due to Diodrast in the distribution of the external carotid artery and was never seen following injections of the internal carotid alone. Following percutaneous injection in the human, this swelling can be mistaken for local extravasation of blood or Diodrast. This might even explain the laryngeal stridor occasionally seen in humans which results from laryngeal edema. These distressing effects in the neck can be prevented by selective injection of the internal carotid artery only.

It has been observed that severe, unilateral head pain may occur in the awake human at the time of injection. In this series the pain was reported as being worse when cool solutions of Diodrast were injected. Likewise, the awake monkeys always reacted more severely to injections of cool solutions. Since it has been shown that such solutions cause maximal vasospasm, this further substantiates the belief that this pain is secondary to the vasospasm.

Hyperpnea is seen fairly frequently in both awake and anesthetized monkeys as well as humans. Respiratory arrest was infrequently seen in animals. Increased lethargy occasionally occurs following injection in both animals and humans. In this series this lethargy was most pronounced in humans with pre-existing CNS damage. No human death has occurred in the experience of the authors, but in this series there were 3 monkeys and 2 cats which died following intracarotid Diodrast. In both cats death occurred abruptly following immediate respiratory arrest at the end of injection. The monkeys expired at periods ranging from 12 to 48 hrs. after an experiment consisting of multiple Diodrast injections.

When any vasomotor or EEG effect was produced it was always more marked with 70 per cent than with 35 per cent Diodrast. On occasion, only the 70 per cent solution produced the changes described. It would appear that the effects are roughly proportional to the concentration of the dye. The evidence for cumulative effects on repeated injections is less clear. Marked individual variation in the tolerance to Diodrast was present, and in one monkey 400 mg./kg. of body weight was injected without permanent residua. This is four times the “equivalent human dose” as calculated by Heathcote and Gardner. Factors influencing cumulative effects include type of anesthesia, presence of organic changes in the CNS, concentration and volume of Diodrast per injection, interval between injections, presence or absence of cardiorespiratory effects, and individual variation. In view of the multiplicity of factors, it is not surprising that no definite correlation could be established in this series between the total amount of Diodrast injected and the effects observed. In studying the various effects here described, any possible cumulative effects were felt to be eliminated. In spite of an attempt at detailed statistical analysis, no precise correlation can be drawn between CNS changes and total dosage. However, a crude qualitative impression exists that the described changes are somewhat greater following repeated injections.
DISCUSSION

In a recent monograph on carotid angiography based on over 2000 cerebral angiograms using Diodrast, Torkildsen\textsuperscript{19} has listed some of the various complications that may occur, but has failed to determine their frequency by detailed analysis. That Diodrast angiography is not completely innocuous is indicated by the recent report of Dunsmore, Scoville and Whitcomb\textsuperscript{4} who report a 14 per cent incidence of complications in their series of 108 cases. They also point out that the previous literature emphasizes the relative safety of the procedure. Previous investigations regarding the mechanism of these complications in the use of Diodrast have been scanty.

The present investigation on monkeys and humans indicates that intracarotid Diodrast has two effects on the brain: (1) a direct toxic action on the nerve cell; and (2) a protective vasospasm minimizing the amount of toxic substance reaching the nerve cell in any given period of time. Angiospasm at the time of Diodrast injection has been previously described by Broman and Olsson\textsuperscript{5} who observed that there was no pial circulation for 3 to 8 sec. after injection of the contrast medium. The present findings would agree with this except in detail. Vasoconstriction has also been observed by Holm\textsuperscript{8} in the cranial circulation and by Edwards and Biguria\textsuperscript{5} during femoral arteriography with Diodrast.

Broman and Olsson demonstrated marked changes in the blood-brain barrier after intracarotid Diodrast in animals, using the trypan blue technique. This and certain other dyes will not, under normal circumstances, pass through cerebral vascular membranes. Following endothelial damage the permeability is increased and the dye then stains the damaged portion of the brain. They illustrate that intracarotid Diodrast causes the injected hemisphere to stain a bright blue. These authors felt that the Diodrast damage to the brain in their series was a pure injury to the blood-brain barrier without edema, hemorrhage, necrosis or thrombosis. However, their evidence would indicate that some direct cytotoxic effect does exist since they describe increasing clinical signs in the presence of regressing changes in vascular permeability.

Using Evans blue, Bassett, Rogers and Cherry\textsuperscript{1} demonstrated in dogs and rabbits that similar increases in the permeability of the blood-brain barrier were produced by Diodrast. They point out that pH of the injection medium is not a major factor and that the osmotic pressure of the injected solution is not solely responsible since injection of 20 per cent saline, which has the same tonicity as 35 per cent Diodrast, causes slightly less change in the permeability than does Diodrast. These authors, however, deny the existence of massive vasospasm.

Bloor, Wrenn and Margolis\textsuperscript{2} using copper phthalocyanine dye in rabbits, likewise demonstrated changes in permeability of cerebral vessels and showed pathological changes in endothelium and also in nerve cells. This latter finding is in direct contrast to the report of Kristiansen and Cammermeyer\textsuperscript{9} who failed to observe any pathological changes in the brain following carotid
angiography with Diodrast. Bloor et al. also point out that EEG changes parallel the dye transfer and pathological changes. EEG changes somewhat similar to those reported here have also been described in dogs and humans by Heimburger and Freeman.7

The correlation between the alterations in vascular permeability and the EEG changes is not entirely clear. In the present experiments when the vasospastic element was minimized by stellate block and warm solutions, the immediate EEG changes were much more marked and occurred more rapidly than might be anticipated if these alterations in neuronal activity were due solely to increased vascular permeability. On the other hand, late effects, as judged by the EEG and clinical complications, might well be explained by both the direct cytotoxic effect and the changes in the blood-brain barrier, the relative contribution of each being unknown. That changes in the blood-brain barrier may occur without the development of cerebral edema has been pointed out by Broman and Olsson,3 and this agrees with our observations that there is no late development of increased spinal fluid pressure.

Certain clinical applications seem warranted on the basis of our results. Warm solutions of Diodrast produced less vasospasm but greater EEG changes than cool solutions, suggesting that a greater cytotoxic effect was produced. Temperature alone is not the critical variable since neither warm nor cool intracarotid saline produces any vascular effect or EEG changes. At the present time we are not able to judge whether the increased activity of warm Diodrast is due to chemical activation or to some other factor. In any case, the warming of Diodrast to body temperature prior to injection would seem to be contraindicated.

Since the cerebral effects of intracarotid Diodrast are startlingly increased after stellate block, measures designed to minimize cerebral vasospasm during Diodrast injection are also contraindicated. Although better radiological contrast might be achieved by these measures, it would be at the expense of increased cellular damage. However, this does not alter the indications for stellate block after angiography in selected cases.

It should be emphasized that the changes here described do not fall into the category of changes seen clinically that are classified as “complications.” It has already been reported that such complications representing major CNS damage do occur in about 14 per cent of clinical cases (Dunsmore, et al.4). However, clinical methods in current use are so crude that fine abnormalities of structure or function cannot be determined. It is these finer abnormalities caused by intracarotid Diodrast that have been described in this experimental series. Thus, the fact that major complications occur relatively infrequently should not obscure the fact that some diffuse damage including neuronal death may occur almost routinely as the result of Diodrast angiography. These possible hazards must therefore always be weighed against the information gained by angiography in any particular patient. The obvious solution would be a contrast medium that does not possess
the toxic properties of Diodrast. Various new substances are in preparation which will be screened by laboratory methods for possible use in carotid angiography.

CONCLUSIONS

1. Diodrast is far from an ideal contrast medium for cerebral angiography. Two primary effects of intracarotid Diodrast are demonstrated: (a) a direct toxic action on the nerve cells; and (b) a protective vasospasm minimizing the cytotoxic effect.

2. Initial rapid vasoconstriction followed by longer lasting vasodilatation was demonstrated visually and photographically in monkeys. Quantitative continuous recording of spinal fluid pressure during angiography demonstrated an initial rapid fall in pressure followed by a longer lasting rise corresponding to the observed vasomotor changes.

3. Continuous recording of the electroencephalogram during intracarotid Diodrast in both monkeys and humans demonstrated multiple abnormalities which seem to be due to a direct toxic action of diodrast on the neurones.

4. Warm solutions of Diodrast produced less vasospasm than cool. Unilateral stellate block also abolished the phase of vasoconstriction. After this protective vasospasm had been minimized by either of these means, intracarotid Diodrast then produced far greater abnormalities in the electroencephalogram.

5. Some type of electrocardiographic or pulse rate abnormality was routinely produced in both monkeys and humans during angiography. These seem to be the result of central nervous system changes.

REFERENCES

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