whereas the cataracts resulted from exposure of the head region, the absence of lethal radiation disease may have been owing to a shielding of much of the rest of the body. Five of the patients had very little, if any, radiation sickness, and the symptoms in the others may not have been caused by the radiation. Yet all of them had profound epilation of the head, which was undoubtedly a radiation effect. It is possible that the three standing in front of the streetcar were protected in the lower halves of their bodies by the metallic baseboard below the car windows.

The frequency of atom bomb cataracts now, or to be expected in the future, cannot be stated at present, since practically all the cases of cataracts here cited were discovered through highly selective methods. However, it may be noteworthy that 1000 persons, believed to be a cross section of the survivors, who were within two kilometers of the hypocenter and in the open (including 16 persons within one kilometer), were examined and no case of radiation cataract was found. (Although all these persons were out of doors at the time of the explosion, the amount of shielding by buildings, posts, other persons, etc. could not be satisfactorily determined.) Among an additional 231 persons within one kilometer of the hypocenter, who were either in the open or in wooden buildings at the time of the explosion, there were found five cases of radiation cataracts (included in the ten mentioned above).

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## Cyclotron-induced Radiation Cataracts

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Although it is impossible now to make a complete or final report on the cyclotron-produced radiation cataracts, it seems desirable to publish a preliminary survey of the situation as it now appears. This survey should serve as another warning to research personnel and administrators in the field of high energy particles and it also should serve to indicate how large is the area of ignorance regarding radiation effects on higher organisms.

Early in December 1948 it became known that at least five nuclear physicists of average age 31 were afflicted with incipient cataracts. An *ad hoc* committee set up by the Division of Medical Sciences of the National Research Council arranged for questionnaires to be sent to all the high voltage laboratories of the country where comparable exposure risks might have been incurred, and a considerable body of preliminary data became available by this means.

Arrangements were made to bring together as many as possible of the afflicted men, along with a few other especially qualified and interested individuals, to discover and compare if possible the common denominators of their experience and to make careful comparable medical examinations. A meeting was held in Washington, D. C., January 16 and 17, 1949, under the auspices of the Division of Medical Sciences, National Research Council, with the support of the U. S. Atomic Energy Commission. On January 18, eleven of these men were examined at the Wilmer Ophthalmological Institute, Johns Hopkins School of Medicine, by Drs. Alan Woods, Jonas Friedenwald, and Algernon Reese, who concurred in the following findings:

1. Ten of these patients showed opacities in the lenses.

2. The patients fell into three general groups as follows:

*Group A (3 men)*: All showed severe changes in the posterior cortex of the lens, consisting of thick saucer or disk-like opacities, together with slight subcapsular or anterior cortical haze. The capsule and nucleus of the lens were clear, and there was no other pathology found in these eyes (except postoperative changes in one individual). In all vision was reduced.

*Group B (4 men)*: Slight to moderate changes in the posterior cortex of the lens. These changes consisted in whitish opacities with a definite tendency to saucer or disk-like formation, in the milder cases accompanied by a golden reflex and occasionally by slight iridescence. Again there was occasionally slight haze in the anterior cortex, and a few vacuoles. The media and capsules were clear, and there was no other pathology in the eyes. In these men, vision was either normal or only slightly reduced.

*Group C (3 men)*: Minimal, insignificant, and doubtfully relevant changes. The findings consisted in a thin lacy opacity in the posterior cortex and occasional punctate dots, and capsular iridescence. The thin lacy opacity, when observed, lay in the posterior cortex with a suggestion of disk formation, which made it a little suspicious. There was, however, considerable doubt in the minds of all three examiners whether these slight changes were definitely pathological. There were no other changes observed in these eyes.

3. All the observed changes followed the same general pattern, showing different degrees of severity. Furthermore, this common picture conforms to the general picture of roentgen-ray and radium cataracts. In the absence of other recognized causes, and with the common denominator of exposure to cyclotron irradiation, it appears logical to attribute these lens opacities to this cause.

Table 1 summarizes the experience of these men.

The men are listed in the table in the order of severity of symptoms. The first three men have what can be termed a severe handicap. The next four are afflicted to a degree which does not at present interfere markedly with daily life. The remaining three have a minimal affliction which does not cause appreciable handicap. It was noted, however, that the severe cases did not fully develop until about three years after the radiation was received. Hence, some of the men may in the future show a more severe pathological condition arising from radiation already received. Since there has been no evidence of damage to the retina, it would appear that there is a good prognosis for successful surgical intervention in the severe cases. Indeed, in the interval between January and July 1949, cataracts were successfully removed from two of the individuals concerned. Thus, it

TABLE 1

| Patient | Probable date of exposure | Estimated total exposure to neutrons (n-units) | Duration of exposure in weeks | Visual acuity | | | |
|---|---|---|---|---|---|---|---|
| | | | | Uncorrected | | Corrected | |
| | | | | Left | Right | Left | Right |
| 1 | 1944 | 135* | 200 | LP† | ... | LP† | 20/200 |
| 2 | 1943–44 | 80 | 25 | ... | ... | 20/100 | 5/200 |
| 3 | 1943–44 | 80 | 25 | 20/100+2 | 20/70–1 | 20/20/3 | 20/40–2 |
| 4 | 1941–47 | 30–40 | 250 | 20/40 | 20/20–1 | 20/20–1 | 20/20 |
| 5 | 1947–48 | 30–100 | 10 | 20/40 | 20/70 | 20/15 | 20/15 |
| 6 | 1947–48 | 20–100 | 30 | 20/40 | 20/30 | 20/20 | 20/20 |
| 7 | 1943–44 | 10 | 25 | 20/20 | 20/50 | 20/20 | 20/15 |
| 8 | 1939–42 | 70 | 100 | 20/20–4 | 20/20–3 | 20/15–1 | 20/15 |
| 9 | 1947–48 | 4–25 | 10 | 20/70 | 20/20 | 20/40 | 20/15 |
| 10 | 1938–40 | 15 | 80 | 20/20 | 20/20 | 20/15 | 20/15 |

* Patient 1 had one acute exposure of 35 n.
† LP = Light projection only.

appears that the afflicted men will not lose their vision irretrievably. All of the men involved are in reasonably good spirits and are carrying on productive activities professionally.

The accurate measurement of neutron intensities and energies is a rather difficult problem. To date most measurements have been made using equipment originally designed for use with x-rays. When a 100-r Victoreen chamber is exposed to fast neutrons and a full-scale reading is obtained, the instrument is said to indicate an exposure of 100 n. In many experiments it is convenient to use a 25-r Victoreen chamber and the resulting dose is expressed in N-units. In general, tissue dose in roentgen equivalent physical equals 1.5 n equals 2 N.

It is difficult today to estimate exposure occurring three to nine years ago. The individuals involved made independent calculations of their own exposures. The cumulative doses estimated were surprisingly low with a median dose 50 n.

At the time these men were receiving the exposure that led to cataracts, most were being given periodic blood examinations. In no case was there a change in blood picture to give a dramatic warning of overexposure to radiation. In only two cases was there a mild epilation. In general neutron irradiation of the head was greater than that to the whole body. Perhaps this accounts for the failure to observe blood changes.

It seems probable that the causative agent of the injury in most cases was chronic exposure to neutrons in the range 0-20 Mev. Evidence for this statement is rather indirect. The high energy radiation from the cyclotrons involved is principally neutrons and gamma rays. In most cases, the intensity as measured in an ionization chamber shows slightly more neutron than gamma-ray effect. Since not nearly enough gamma-ray intensity is present to produce cataracts, elimination leaves neutrons. The possibility does exist that the neutron effect might be enhanced by radiofrequency effects or by motion in the magnetic field of the cyclotron. However, the discovery of cataract production in mice by both cyclotron- and nuclear reactor-produced neutrons seems to make such complicating suggestions unnecessary.

In most cases, persons involved received their neutron exposure while at an angle of about 90° to the direction of a 8-to-16 Mev deuteron or proton beam. Target materials were variable and few measurements have been made by nuclear physicists of the particles emitted when particles of this energy strike targets of any kind. In most cases, there was little moderating material between the source and the lens.

A survey of the literature with respect to radiation cataracts reveals that considerable qualitative but little quantitative information is extant regarding cataracts induced by x-rays and gamma rays. Leinfelder and Kerr (*2*) have published one of the best studies of roentgen-ray cataract in humans. While their data involve a small number of cases, the indication is that approximately 2500 r is required to produce the effect. From supplementary studies on rabbits they found soft x-rays to be more damaging than hard x-rays, and that small doses of x-rays given over a period of time were less injurious than an equal acute dose.

Very little is known regarding cataracts produced by neutrons. The paper of T. C. Evans (*1*) provides the best information and indicates that the biological effectiveness of chronic doses of neutrons in producing lens abnormalities in mice may be as high as 8–40 times as great as x-rays. Insofar as the data from human eyes can be interpreted, it seems likely that with chronic exposure, the ratio of rem to rep for neutrons may likewise be as high as 10–40; that is, the ratio of roentgen equivalent man to roentgen equivalent physical may be as high as 10–40. Results given by R. S. Stone (*3*) are in accord with high biological effectiveness of chronic neutron exposure.

It should be emphasized that these figures for biological effectiveness of neutrons are merely the best estimates that incomplete and fragmentary data permit. In view of the implications of this finding, it is extremely important that further and more quantitative information be gathered from both animals and man.

It appears probable that if complete examination were made of all persons who have worked with cyclotrons, a further small group of afflicted individuals might be discovered. Most of the additional cases would probably

be found not to be markedly handicapped. It is also possible that other portions of the body may be relatively highly affected by neutrons. For instance, the Evans experiments suggest, in mice, a selective sensitivity of the gonads as well as of the lens.

It is perhaps worth while to list a few of the areas of ignorance which have been highlighted by this unfortunate episode:

1. The exact causative agent is not definitely known;
2. The dose is imperfectly known;
3. Almost no systematic neutron research has yet been performed on organisms larger than a mouse;
4. There is little knowledge extant of what other organs of the animal may be especially susceptible to damage under special circumstances;
5. The concept of the rem (roentgen equivalent man) for neutrons and indeed for other new types of radiation is probably of limited value, since the conversion factor varies with tissue.

The National Research Council has appointed a Committee on Radiation Cataracts which is collecting additional information regarding others who have been exposed to neutrons. The committee will also conduct follow-up studies of those already known to be injured. Communications should be addressed to Philip S. Owen, M.D., Executive Secretary, Committee on Radiation Cataracts, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

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## Sodium 2-Methyl-4-Dimethylaminophenylphosphinite, a Probable Methyl Donor[1, 2]

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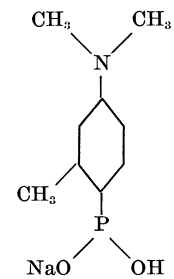
Previous investigations on biological methyl donors have shown evidence of a rather limited number of substances exhibiting donating properties, most of them being N-methyl compounds like choline. It is interesting to note that such N-methyl compounds, having the ability of giving methyl groups intact, show a similar basic structure—namely, they have their labile methyl groups bound with a quaternary or positive nitrogen (choline, betaine, dimethylethyl-β-hydroxyethylammonium chloride [6], tetramethylammonium formiate, methyltriethanolammonium iodide [2], etc. These observations fit in with the theory described by Du Vigneaud (3) based on the different ability of transmethylation shown by partially methylated aminoethanols and choline.

The relationship existing between structure and methylation capacity, described in the N-compounds cited, appears worthy of being generalized (2). Ciusa claims also that methyl compounds of arsenic, selenium, oxygen, and sulphur (2) may act as methyl donors when methyl groups are bound with electropositive atoms. A confirmation of this is obtained by experimental investigations on sodium cacodylate, and particularly in recent studies by Du Vigneaud on dimethylpropiothetin (4) and dimethylthetin (5).

A few recent observations from this laboratory concerning sodium 2-methyl-4-dimethylaminophenylphosphinite, which is used largely in therapy, are not in agreement with these assumptions.




The administration of this substance to human subjects, in normal conditions, causes a remarkable rise in urine elimination of $N_1$-methylnicotinamide, a product of the irreversible methylation of nicotinamide, introduced with diet and chosen as a test of the methylation activity (2).

We do not intend to take into consideration here details of technique, which are to be published later; we are reporting, instead, a few data obtained in this investigation, pointing out that the experiments have been performed on ourselves and on laboratory personnel, fed a rigorously standard diet, under normal conditions.

The values of N-methylnicotinamide reported herein refer to 24-hr urines. The administration of sodium 2-methyl-4-dimethylaminophenylphosphinite in a single therapeutic dose (30 mg), causes an immediate urinary increase in $N_1$-methylnicotinamide as seen in results in Fig. 1. The increase, in this case, is approximately 60%, while in other human subjects it has reached even higher values.

When the administration of the substance under observation is continued for several days in even small doses (15 mg), the elimination of $N_1$ is maintained constantly elevated above the normal, returning to the initial values as soon as the treatment is terminated. We do not believe the action of sodium 2-methyl-4-dimethylaminophenylphosphinite is attributable to a simple activation of methylation processes. The increased elimination, in fact, remains even when the subject is preventively treated and also treated during the experiment

[1] We are greatly indebted to Mr. Cesare Barbieri and to the American Committee, University of Bologna, New York, for donation of the Beckman DU Spectrophotometer used in this investigation.

[2] The experiments have been performed with sodium 2-methyl-4-dimethylaminophenylphosphinite supplied by Consorzio Neoterapico Nazionale, Roma.