STUDIES IN THE REACTION OF THE EYE TO THERMAL, CHEMICAL AND RADIATIONAL HAZARDS.

A Thesis

presented for the Degree of Doctor of Medicine

by

Robert Leishman, M.B., Ch.B., D.O.M.S.

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"The future progress of ophthalmology will depend upon increase in knowledge of the physiology of the eye, and the further advance in the treatment of ocular diseases will in all probability be brought about by the application of discoveries by the chemist and the physicist rather than by any considerable improvement in operative technique. The physician, however, is not a pure chemist or a pure physicist, or even a pure physiologist. He is on a different platform from that occupied by any other science student, and must study every medical problem from the standpoint of the body as a whole. He must adapt for his own purposes the advances of science in general, and more especially those of that fundamental science - biochemistry. The causal factors of disease, whether of bacterial or of metabolic origin, are essentially chemical in character." - Maitland Ramsay.

PREFACE.

This Thesis is based upon work carried out by the author as an Experimental Officer during 1942-43 at the Chemical Defence Experimental Station, Porton, to which he was seconded from the Royal Navy. This war-time experience has been supplemented by a survey of clinical cases treated at the Tennent Institute, Western Infirmary, Glasgow. I am indebted to Surgeon Captain A. Fairley, O.B.E, R.N., Director of Physiological Research, Porton, and to Prof. W.J.B.Riddell, Professor of Ophthalmology in the University of Glasgow for their interest and encouragement.

Security restrictions have been removed from those parts of the Thesis which deal with matters which were secret during hostilities. Nothing has been included which comes under the Official Secrets Act.

STUDIES IN THE REACTION OF THE EYE TO THERMAL, CHEMICAL AND RADIATIONAL HAZARDS.

SUMMARY.

Chemical injuries are often described as burns, a term which, in its more general application, is used to include the lesions produced by physical as well as chemical agencies. In order to apply the experience gained in the relatively limited field of chemical injuries to the more usual types of ocular burn met with in civilian hospital practice, it was decided to make an analysis of all cases of burns of the eye occurring in a large hospital population. I am indebted to Professor Riddell for placing at my disposal for this purpose, the case-records of all patients examined on account of ocular conditions in the Tennent Institute, Western Infirmary, and I have taken the opportunity of putting clinical impressions to the test by applying statistical methods in this analysis. This forms the subject matter of Part 1, together with a short discussion of a group of cases of accidental injury to the eyes caused by mustard gas vapour. I am again indebted to Professor Riddell for access to his records of these cases, originally prepared for the Ministry of Supply.

The Second World War gave an impetus to the study of the biological effects of certain chemical substances which were considered potentially useful in warfare. I was fortunate in having the opportunity to take part in experimental research designed to determine the effects of such substances on the eyes of animals. It was undesirable

for obvious reasons, that the results of these experiments should be published during the war, but restrictions have now been removed and the work is incorporated in Part 2 of this Thesis.

The available literature has been reviewed and assessed in the light of my own experience. Certain papers selected for more detailed consideration are presented in Part 3.

A discussion of ocular burns with particular reference to the theoretical and biological aspects of the subject is based on observations contained in the preceding parts. This forms the final section.

STUDIES IN THE REACTION OF THE EYE TO THERMAL, CHEMICAL AND RADIATIONAL HAZARDS.

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PART 1.

"As in Mathmeticks, so in Natural Philosophy, the Investigation of difficult Things by the Method of Analysis, ought ever to precede the Method of Composition....."

Sir Isaac Newton., Opticks, 1730

PART 1.

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PART 1.

STATISTICAL ANALYSIS OF BURNS OF THE EYE FOUND AMONGST A SERIES OF HOSPITAL PATIENTS.

1. Review of the Data.

During the years 1936-45, 14,234 ophthalmic cases were recorded in the Tennent Institute of Ophthalmology. This total includes out-patients attending the department and patients examined in the wards of the Western Infirmary. From amongst this number, 96 patients were examined on account of the effects of burns in relation to the eye; the complete data extracted from the case-records of this series of 96 cases are shown in Table 1.

Certain limitations were apparent in the data at the outset. For instance, it would have been of interest to know where the accident occurred, whether at home or in the course of employment, but observations on this point were so infrequent that they have been omitted. It would also have been of interest to know the nature of any first-aid measures which were taken immediately after the accident, and the interval of time which elapsed before first-aid was applied, but here again the records were insufficient. In the case of other factors, such as visual acuity, while the records are not complete, the recorded observations are of sufficient frequency to be of value. When an observation was not recorded, this has been shown as N.R. in the

appropriate cell of the table. Certain other entries call for explanatory comment. The injuring agents have been classified according to the type of injury as well as the recorded cause. Case 2 has been shown as "electrical flash (thermal)" whereas Case 74 appears as "electrical flash (radiational)". The distinction is clear from the notes in the respective case-records. Column 8 gives a numerical assessment of the severity of the injuries for the purposes of the analysis. The figures shown as "Units of Severity" represent the total number of days of in-patient treatment, or the total number of days of out-patient attendance, or the sum of these values, according to which is applicable in the particular case.

2. The Proportional Rate of Occurrence of Burns.

As has been stated, 96 cases of burns related to the eye occurred amongst 14,234 ophthalmic patients during the period 1936-45; this is equivalent to a proportional rate of 0.67%. It is not possible to state the true incidence relative to the general population since the population at risk is not known.

3. Classification of the Data.

On a preliminary perusal of the data the material was found to be heterogeneous and it was apparent that classification would be necessary before statistical methods could be applied. In two cases (serial numbers 17 and 32; Table 1.) examination revealed no abnormality. These cases have been excluded from the following statistical analysis; their exclusion does not affect significantly the

proportional rate calculated above. The remaining 94 cases were found to fall into two groups:-

(1) Cases of recent injury to the region of the eye... 87
(2) Cases of ocular complications of burns..... 7

4. Analysis of Cases of Recent Injury -- Group I.

A. Analysis of the Main Factors.

(1) Frequency Distribution. The frequency distribution of these cases over the ten year period is shown in Table 2.

The question might be raised as to whether there is any significant alteration in the frequency of occurrence of these injuries during the war years 1939-45 in comparison with the years 1936-38. The data have been regrouped for this purpose in Table 3. The proportional rate shows a decrease from 0.73% in the prewar period to 0.57% during the war years. Applying the χ^2 test of significance, a value of 1.097 is obtained for χ^2; since there is one degree of freedom this corresponds to a probability value between 0.30 and 0.20, indicating that the difference in the proportions could reasonably be accounted for by chance.

(2) Age distribution. Whether the age of the patient influences the severity of these injuries or not, is a question worthy of investigation. Differences in tissue resistance might occur in the very young and the very old as compared with the intermediate age-groups. In attempting to answer this question from the data it will be observed that the whole series can be divided into two groups; one group receiving in-patient treatment, and a second group

receiving out-patient treatment only. The observed frequency distribution according to age in both groups is shown in Table 4. It could reasonably be assumed that the group receiving in-patient treatment would, in general, tend to include the more severe cases. On this assumption the difference in distribution between the two groups which is apparent in Table 4 might lead to the inference that there is a relative increase in the number of severe cases in later age groups. It would be unsafe to come to such a conclusion, however, before attempting to determine whether a difference of this order might be expected to occur frequently by chance in a series of similar observations. The χ^2 test is again applicable after the age-groups have been combined as shown in Table 5. χ^2 is calculated to be 0.0126; since there are two degrees of freedom, this corresponds to a probability value of about 0.99. This value is not significant, so there is no reason to attribute the difference observed between the groups to anything but chance. By re-arranging the data as in Table 6, it appears that the majority of such injuries occur during the years of life usually occupied in gainful employment.

(3) Sex Distribution. If the observations shown in Table 7 were interpreted on a percentage basis alone, the results would be misleading. Females account for 12.6% out of the whole series of 87 cases. In the in-patient group they account for only 6.7%, whereas in the out-patient group they account for 15.8%, a difference which might appear to be significant. If the χ^2 test is applied to the data in

Table 7, a value of 1.49 is obtained for χ^2; since there is one degree of freedom, the probability value lies between 0.30 and 0.20, which is not significant. It will be observed that one of the cells in Table 7 contains a value of less than 5. This is known to affect the value calculated for χ^2 in such a way that observed differences appear to be more significant than in fact they are. Since the probability value obtained does not reach the conventional level of significance, the test is valid in this instance; but if the value had been significant it would have been necessary to adjust the data in the table in accordance with Yates' correction for continuity, before applying the χ^2 test. It is safe to conclude, however, that the difference in distribution between the sexes observed in Table 7 may well be accounted for by chance.

Relationship between Age and Sex. To consider the distribution of cases of recent injury with relation to both age and sex, the data may be arranged as shown in Table 8. There appears to be a marked difference in age distribution between the sexes, and to test this impression, the observations are re-grouped in Table 9. The same data are shown in Table 10 after application of Yates' correction. The values in each cell are altered by 0.5 in such a way as to make them more alike, while the marginal totals remain unchanged. By calculation, $\chi^2 = 5.11$; and since there is one degree of freedom, this corresponds to a probability value of between 0.05 and 0.02. There is good reason to assume, therefore, that something other than

chance is operative in causing the difference in age distribution between the sexes.

(4) Severity of the Injuries. Before discussing the nature of the injuries and their localization it is desirable to arrive at some numerical method of assessment of their severity. This is a difficult problem since it implies assessing features difficult of measurement, and comparing features of different lesions; obviously it is not possible to do so with scientific accuracy. Fortunately, however, all that is necessary for the present purpose is to select some scale of measurement for the severity of the lesions which will indicate numerically the facts recorded in the data, and which will be sufficiently accurate to allow a rough comparison to be made between the various injuring agents with regard to the severity of the lesions they produce. The simpler and more objective such an assessment is, the better.

From Table 1 it is found that in six cases within the group of recent injuries, evidence is recorded of permanent residual damage to the eye as a result of the injury.(Serial numbers - 8, 9, 14, 23, 27, and 93.) These defects range from corneal scars associated with normal visual acuity to loss of an eye, but all the eyes have suffered permanent structural damage. Any scale of severity values selected, if valid, must discriminate clearly between this group of six cases and the remainder.

Considering first the group of cases receiving in-patient treatment, the total number of days which the

patient remained in hospital could be taken as a simple objective estimate of severity in each case. One case (Serial number - 79) is omitted from consideration in this group since the duration of hospital treatment is not known. The resulting series of 29 cases includes all six cases showing permanent structural damage. Table 11 shows the observed frequency distribution for the series of in-patient cases arranged according to periods of seven days.

In the case of patients receiving out-patient treatment only, the total number of attendances at hospital could be taken as an estimate of severity. The frequency distribution for this group of cases is shown in Table 12 .

From consideration of Table 11 and 12 it will be apparent that in neither group do the observed frequencies have a normal distribution, but that they appear to decrease after the fashion of series distributions. Since one of the variates is continuous, the Poisson series is not applicable in either case. Nor do they appear to give a good fit when tested by the general formula $y = Cx^{-n}$, in order to determine whether y varies inversely as a power of x. When tested to determine whether the observed values conform to an exponential law of general formula $y = Ce^{-kx}$, it is found that values of log y plotted against x do not appear to approximate to a straight line. Since the observations in each group are relatively few and do not appear to give a good fit to any of the commoner types of series distributions, and since the exact determination of a formula to describe the distribution is not of immediate importance, the matter will be left there having called

called attention to the fact that the distributions are far removed from that of the normal curve.

Test of Severity Values: Comparison of Means of Small Samples. Although the observed frequencies are not normally distributed, the severity values in the two groups may be tested by the method of comparison of the means of small samples. On the hypothesis that the two groups are random samples from the same population, and taking the number of days of in-patient treatment as an estimate of severity of the lesions, the group of six cases showing permanent structural defect may be compared with the remaining 23 cases receiving in-patient treatment.

Estimation of the statistic t, when

$$t = \frac{\text{Difference between the Means}}{\text{Standard Error of the Difference between the Means}}$$

will show how often by random sampling, differences would be found between the means as great or greater than the observed differences. The data are shown in Table 13. Thus:-

Mean for 6 cases with residual defect.....	22.5
Mean for 23 cases without residual defect.....	9.783
Difference.....	12.717
Sum of squares of deviations from mean for cases with residual defect.....	1089.5
Sum of squares of deviations from mean for cases without residual defect.....	2179.937
Combined sum of squares.....	3269.437
Divisor (Sum of degrees of freedom) = (23-1) + (6-1).....	27.0
Mean Square (Variance) = $\frac{3269.437}{27}$ ..... =	121.09
Estimated standard deviation = $\pm\sqrt{121.09}$ =	$\pm$ 11.004

Standard error of mean for cases with residual defect..... $= \frac{11.004}{\sqrt{6}}$

Standard error of mean for cases without residual defect..... $= \frac{11.004}{\sqrt{23}}$

Standard error of difference between means..... $= \pm\sqrt{\left(\frac{11.004}{\sqrt{6}}\right)^2 + \left(\frac{11.004}{\sqrt{23}}\right)^2}$

$$= \pm 11.004 \sqrt{\frac{1}{6} + \frac{1}{23}}$$

$$= \pm 11.004 \sqrt{\frac{29}{138}}$$

$$= \pm 11.004 \sqrt{0.21}$$

$$= \pm 11.004 \times 0.46$$

$$= \pm 5.062$$

Then $t = \frac{\text{Difference}}{\text{Standard error of difference}} = \frac{12.717}{5.062} = 2.511$

To enter Fisher's Table of t, n = 27; for this value of n, a t value of 2.511 corresponds to a probability value of between 0.02 and 0.01, which is significant if the conventional level of significance (0.05) is accepted. It appears, therefore, that the assumption that the two groups are random samples from the same order of severity values is not valid so far as the means are concerned.

Test of Severity Values: Fisher's Exact Method.

It is desirable to check this result by other methods in order to obtain a better appreciation of its accuracy. The χ^2 test is not applicable in this case since it depends on a distribution of normal type. The Table of χ^2 gives the area of the tail of a continuous curve, and Yates' modification tends to overcorrect the exaggeration of significance due to applying a table of continuous distribution to data which are

discontinuous. In ordinary use the treatment of frequencies by means of the χ^2 is an approximation which is useful on account of its simplicity. In fourfold tables, however, the probability can be determined by an exact method (Fisher 1938) which does not depend on the normal curve as in the case of χ^2. Since the frequency distributions of the severity values which have been observed show a marked departure from the configuration of the normal curve, Fisher's exact method will be used subsequently in all calculations involving severity values. To confirm the result obtained by the method of comparison of the means of small samples, in Table 13, the same two groups of cases may be tested by the exact method using the same severity values. The data consist of a fourfold table, Table 14.

When the marginal frequencies are known, the probability of any observed set of entries is

$$\frac{(a+b)!\ (c+d)!\ (a+c)!\ (b+d)!}{n!} \cdot \frac{1}{a!\ b!\ c!\ d!}$$

Substituting the frequencies shown in the table into this formula we obtain the probability of the observed frequencies. If the probabilities of the next two more extreme sets of frequencies which might have been observed are added to the value for the observed frequency, then without any assumption or approximation, the table observed may be judged significantly to contradict the hypothesis of proportionality if the result is a small quantity (Fisher 1938).

Substituting in the formula:-

$$\frac{24!\ 5!\ 6!\ 23!}{29!}\left(\frac{1}{2!\ 3!\ 3!\ 21!}+\frac{1}{2!\ 4!\ 22!}+\frac{1}{1!\ 5!\ 23!}\right)$$

the value obtained is 0.046. This shows that if the hypothesis of proportionality were true, observations of the kind recorded would occur about one in 22 times. This result is significant, but the value lies close to the conventional level of significance of 1 in 20.

It could be argued that such values do not differentiate sufficiently between two essentially different groups of cases. It must be clearly understood that, by such an argument, it is not intended to call in question the results of the tests, but rather the level of significance which has been chosen. In the former test (shown on pages 10 & 11) a difference in variance between the groups may enhance the value of t obtained. The test, therefore, is decisive, if the value of t is significant. (Fisher 1938). When the significance of the difference between the variances is tested directly by calculating the statistic z (the difference of the natural logarithms of the standard deviations), the calculated value of 0.3946 is found to be insignificant by comparison with the 5 per cent point of the distribution of z. This shows that the significance of the t value obtained is unlikely to be produced by a difference between the variances only.

Severity Values tested by χ^2. It is of interest to note the result obtained when the χ^2 test is applied to frequencies so far removed from the normal distribution. When Yates' correction has been applied to the

observed frequencies in Table 14, χ^2 is found to be 3.163; for n = 1, P = 0.076. But since the observed frequencies in three of the cells of the table have a value less than 5, and since Yates' correction has been used, a better approximation may be given by $\frac{1}{2}P = 0.038$. Such a result indicates that something other than chance is operative, but judgment should be suspended since P is greater than, and $\frac{1}{2}P$ is less than, the conventional level of significance. (Mainland 1938).

Units of Severity. On a basis of these tests it was decided to determine a further set of values which would differentiate between the two groups of cases on a highly significant level. For this purpose the sum of the total number of days of in-patient treatment and the total number of out-patient attendances in days was taken as an estimate in the case of in-patients. When the case had not received in-patient treatment, the number of out-patient attendances in days was taken alone. These values are shown in Table 1, column 8, under the heading of "Units of Severity."

Applying these values as an estimate of severity, the group of 6 cases with a residual lesion was compared with the group formed by the remaining 23 in-patients. Statistical tests were found to give the following results:-

Comparison of the Means of Small Samples:- $t = 3.488$, $n = 27$. From the Table of t (Fisher 1938) it is found that with 27 degrees of freedom, the value of t corresponding to a probability value of 0.01 is 2.771. Since the calculated value of t is much greater than this it indicates that the

difference between the means of the two groups is such that it is highly unlikely that the groups are drawn from the same population of severity values.

Fisher's Exact Method:- P = 0.00548. This shows that, if the hypothesis of proportionality stated in Table 15 were true, observations of the kind would be exceptional, occurring about once in 181 times.

The χ^2 Test with Yates' correction:- Data in Table 15. χ^2 = 6.540. For n = 1, P = 0.0105. Therefore $\frac{1}{2}$P = 0.00525 which is a very close approximation to the probability value found by the exact method. Both P and $\frac{1}{2}$P reach highly significant level.

The group of 6 cases with a residual lesion was compared with a group consisting of the remaining 80 cases of recent injury.

The Exact Method:- Table 16. P = 0.00002. If the hypothesis of proportionality were true, the observations in the table would be highly exceptional, occurring about once in 50,000 times.

The values shown as "Units of Severity" in Table 1 will be used hereafter as an estimate of severity in making a rough comparison between the various types of lesion.

(5). Localization of the Injuries.

Localization may be considered in either of two ways; either with regard to the region affected - regionality, or with regard to the side affected - laterality. The data are arranged in Table 17.

It appears that the globe escaped injury in 13 out of 87 cases, and that the cornea was injuried in 40 out of 74 cases in which the eye was involved. The laterality of the injuries amongst 74 cases is shown by the ratio:-

Right eye: Left eye: Both eyes: : 24 : 23 : 27.

The observed odds are approximately 1 : 1 in favour of either eye being affected, and approximately 2 : 1 in favour of a unilateral as against a bilateral lesion. This is in accordance with theoretical expectation on the hypothesis that the distribution of such injuries as regards laterality is entirely due to chance. Let it be assumed that in a very large series of cases of this kind the chances are equal that either the right eye or the left eye may be affected by such an injury. If from such a population with odds of 1 : 1 there are taken at random a number of pairs of eyes, each pair containing one right eye (R) and one left eye (L), then one half of the right eyes will be unaffected (Ro) and the other half will be affected (Rx). For each class of R, half of the left eyes will be unaffected (Lo), and half will be affected (Lx). The theoretical distribution for a very large population with odds of 1 : 1 can therefore be shown as follows:-

		i.e.
50% Ro	25% Lo	25% Ro Lo
	25% Lx	25% Ro Lx
50% Rx	25% Lo	25% Rx Lo
	25% Lx	25% Rx Lx

It is therefore to be expected that if the laterality is due to chance alone, and the chances are equal of either eye being involved, the ratio obtained in a random sample

would approximate to :-

Right eye : Left eye : Both eyes : : 1 : 1 : 1.

The recorded observations appear to be in accord with such an hypothesis, being distributed in the ratio :-

0.98 : 0.94 : 1.09.

It will be shown below, however, that 4 cases of radiational injury are included amongst the 27 cases. In these 4 cases both eyes were affected, a feature related to the insidious nature of this type of injury. If these cases are excluded from consideration, the observed distribution becomes 24 : 23 : 23 corresponding to a ratio of about 1.03 : 0.99 : 0.99, which appears to approximate even more closely to theoretical expectation on a basis of chance alone. But it will be shown in a later section that there is an association between the distribution of these injuries with respect to laterality and the physical state of the injuring agency. Therefore the agreement between the observed frequency and hypothetical expectation is apparent only, and it would be unsafe to draw any conclusion from the above results as to the random character of the sample.

(6) The Nature of the Injuring Agent.

Inspection of Table 1 shows that the types of lesions which are grouped clinically under the heading of burns may be caused by a wide variety of different physical and chemical agents. In the group of recent injuries the agents may be classified broadly as follows:-

(a). Chemical.
(b). Thermal.
(c). Combined chemical and thermal.
(d). Radiational.

The majority of cases fall into classes (a) and (b), and these classes may be analysed further; in the case of chemical agents into acids, alkalis, and miscellaneous chemical substances; and in the case of thermal agents, according to whether the substance was in the solid, liquid or vapour phase. The distribution observed is shown in Table 18.

(a). Chemical:- The acids concerned are both inorganic and organic. Hydrochloric (HCl), sulphuric (H_2SO_4) and nitric (HNO_3) represent the common inorganic acids, acetic ($CH_3.COOH$) and cresylic acids ($CH_3.C_6H_4OH$) the organic. Cresylic is a weak acid; it is a cresol or phenol of toluene and bears a close resemblance to ordinary phenol in chemical properties.

The chief alkalis recorded are caustic soda (NaOH), ammonia (NH_3) and lime ($Ca(OH)_2$). Quicklime (CaO) combines with water with considerable evolution of heat to form slaked lime ($Ca(OH)_2$). Cement and mortar contain slaked lime which has the power to absorb carbon dioxide from the air to form calcium carbonate ($CaCO_3$).

The miscellaneous class includes chemicals which cannot be placed appropriately amongst the acids or alkalis, e.g. tetryl (tetra-nitro-methyl-aniline, $(NO_2)_3C_6H_2N(NO)_2CH_3$) and methylated spirits; proprietary products such as lysol (50% of cresols dissolved in vegetable soap), vim, creosote (on oily distillate from wood tar), and the cosmetic mascara; or other agents of chemical nature but of incompletely specified constitution, e.g. 'disinfectant fluid', 'anaesthetic', and 'mixed chemicals'.

The following frequency distributions show that inorganic acids and lime are the commonest agents in their respective groups.

Acids.		Alkalis.	
Inorganic.....	9	Lime and cement.....	18
Organic.....	4	Caustic soda.....	3
		Ammonia.....	1

(b) Thermal:- The further analysis of this class is shown below, together with the observed frequency distribution.

Solids.		Liquids.		Vapours.	
Hot metal.....	6	Molten metal.....	6	Flame.....	15
Hot charcoal..	1	Boiling tar.....	2	Steam.....	1
		Boiling water.....	2	Compressed Oxygen.....	1
		Molten fat.....	1		

Flame is the commonest individual agent in the thermal class.

(c) Combined chemical and thermal:- When both a chemical and a thermal agent have been operative in causing the injury the case has been shown in this class. In two of the three cases observed, the injury resulted from contamination of the eye with hot inorganic acids; the third injury was caused by the explosion of powdered chemical substances.

(d) Radiational:- All the injuries in this class were caused by exposure of the eyes to the electric arc during welding.

(7) Acuity of Vision.

The relationship between visual acuity and injury

may be regarded from two aspects. In the first place defective vision might be responsible to some extent for the occurrence of the injury. It would be of interest to know, on the other hand, to what extent such injuries are likely to result in permanent visual defect. It was found, however, that the state of visual acuity existing before the injury was usually unknown, and so it was seldom possible to determine whether the injury had caused the reduction in visual acuity. Further difficulty was encountered through the frequent absence of a final record of vision.

For purposes of analysis the cases are divided into two groups with regard to visual acuity, and it is convenient to make the division at the level R.V.= 6/12, L.V.= 6/12. Vision of this level or worse is considered to be defective, while vision better than this is considered adequate. It is appreciated that such an arbitrary division may appear to the clinician to set a very high standard for the 'adequate' group, but this does not affect the validity of the conclusions reached by statistical tests. The data can now be classified as follows:-

Cases with defective vision before injury.....	13
Cases with adequate vision before injury.....	37
Cases with defective vision due to injury.....	3
Cases with defective vision but without evidence as to the cause.....	10
Cases with no record of vision.....	24
TOTAL.....	87.

It will be seen that in 34 cases the data are insufficient. Out of the remaining 53 cases, in 3 only is the evidence

conclusive that the residual visual defect was attributable to the injury, whereas in 13 cases there was a record of visual defect prior to the injury. 37 cases out of 53 recovered adequate vision after the injury.

(8) Treatment.

Experimental work on chemical injuries of the eye has shown that no treatment of the established lesion apart from an antidote or measures directed towards preventing or controlling complications is likely to affect favourably the course of the lesion. The comparative absence of effective antidotes has concentrated interest on the result of thorough first-aid applied immediately after the accident has occurred. Observations on this aspect of treatment are so infrequent in the records as to be of no value in assessing their efficacy. At the same time it is noteworthy that although several different antiseptics have been used in the series of cases, there is no instance in which a particular therapeutic substance has been placed on record as being unsuitable.

B. Relationship between the Main Factors.

Having reviewed the data and classified the cases in relatively homogeneous groups, it is now possible to examine the material for evidence of association between the various factors on which observations are available.

(1) Age in relation to Other Factors.

a. Age and Sex. It has been shown above that there is a significant difference in age-distribution of

these injuries between the sexes. Fewer women appear among the older age groups. One might speculate that marriage reduces the number of women exposed to risk in these age groups, but a determination of the true explanation would entail examination of the age-distribution for both sexes in the whole population at risk.

b. Age and Severity. It has been shown above that there is no significant difference in age-distribution between cases receiving in-patient treatment and those receiving out-patient treatment. If it is true that, in general, the more severe cases are selected for in-patient treatment, then this result supports the conclusion that there is no close association between age and the severity of the injuries. This conclusion may be tested further by comparing the age-distribution with the assessed severity values shown in 'units of severity', and this is done in a dot diagram in Table 19. There is no evidence of any close association between age and severity in these injuries.

c. Age and Localization. Age would not be expected to affect the localization of the injuries either with regard to the region involved or to the laterality, and the data required to test this contention are contained in Tables 20-23.

Table 20 shows the frequency distribution with regard to laterality arranged in ten-year age groups. Four cases of radiational injury have been shown in brackets in the final column, together with the adjusted total.

Table 21 is derived from Table 20 by combining certain age groups and dividing the injuries according to

unilateral involvement of the right or the left eye. $\chi^2 = 0.235$; for n = 1, P = 0.66; not significant.

If the cases are divided according to whether the injury is unilateral or bilateral, the result obtained is still not significant. $\chi^2 = 0.415$; for n = 1, P = about 0.5 The inclusion of the cases of radiational injury mentioned above does not affect the significance of these results.

In Tables 22, 23(A) and 23 (B) , the data have been similarly treated with regard to the regional distribution of the injuries in relation to age.

In these examples the χ^2 test, with Yates' correction where indicated, has been used as a test for independence between observations arranged in two different classifications in each fourfold table. The results of the tests are shown below the respective tables, and it will be seen that there is no evidence of any close association between age and localization, a finding in accordance with expectation. The tests give no measure of the degree of independence.

d. Age and the Nature of the Agent. Here again it would not be expected that any close relationship would be found to exist between the age of the patient and the nature of the injuring agent. The frequency distributions within the separate classes are shown in Table 24; since the last two columns contain very few observations they are omitted from further consideration. From Table 25, $\chi^2 = 0.544$; for n = 1, P = 0.48; not significant. The two classifications are therefore independent of one another, and do not indicate any association between age and the nature

nature of the agent.

e. Age and Visual Acuity. Age might be expected to show some association with visual acuity. The data which are available in this connection are shown in Table 26. The recorded observations are re-arranged in Table 27 by combining the data contained in certain rows and columns of the preceding table. $\chi^2 = 1.218$; for $n = 1$, P = about 0.27. Thus the classifications in the table are shown to be independent and the differences in the observations may well be accounted for by chance. The data show no evidence of any close association between age and visual acuity.

(2.) Sex in relation to Other Factors.

a. Sex and Severity. Having arranged the data in a fourfold table, Fisher's exact method has been used to test the hypothesis of proportionality. $P = 0.406$; this means that if the hypothesis is true, observations of this kind would occur about 40 times in 100. There is, therefore, no evidence in Table 28 of any close association between sex and severity of the injuries.

b. Sex and Localization. A close association would not be anticipated to exist between the sex of the patients and the localization of the injuries. The data required to test for independence between sex and laterality are contained in Tables 29 - 31(B). The results of the χ^2 test with Yates' correction for continuity are shown below the tables. There is no evidence of association.

Considering unilateral and bilateral injuries amongst males and females from the data in Table 29, it may

be shown in the same way that there is no evidence of association. In this case $\chi^2 = 1.693$; for n = 1, P = about 0.19, and $\frac{1}{2}$P = about 0.095.

Tables 32 - 34 contain the observations with regard to sex and to the regional distribution of the injuries, to which the same statistical treatment has been applied and there is shown to be no evidence of association between the classifications.

c. Sex and the Nature of the Agent. Table 35 shows the distribution of the data after classification. Two of the cells contain no observations; the corresponding columns must be omitted from further consideration. The results obtained from Tables 36 (A) and 36 (B) indicate that there is no evidence of association between the classifications.

d. Sex and Visual Acuity. In this case also no association is to be expected and this is substantiated by the observations in Table 37 - 38 (B).

(3) Severity in relation to Other Factors.

a. Severity and Localization. It might be thought that as more people use the right hand than the left, this might tend to influence the severity distribution with regard to laterality so that right eyes were usually more severely injured than left eyes. The data required to test this contention are contained in Tables 39(A) - 40. By Fisher's exact method the probability value is found to be 0.258, which means that observations of the kind recorded

would be expected to occur 26 out of every 100 times by chance. These data, therefore, cohtain no evidence of association between severity and the laterality of the injury.

It could also be argued that bilateral injuries cause more incapacity than unilateral injuries of the eyes and so might tend to influence severity values based on the number of days of treatment. If this hypothesis were true it might appear as an absence of independence between the classifications shown in Table 41. But by the exact method, P is calculated to be 0.240, showing that the classifications are independent.

Severity of the injuries may next be considered in relation to the region affected. Table 42 gives the frequency distributions observed. Table 43, treated by the exact method, gives a probability value of 0.453 showing that there is no evidence of association between the classifications which are presented. In table 44 lesions involving the cornea are separated from those which have not affected this region. Using the same test, P is calculated to be about 0.000,000,8. If the assumption of proportionality is true observations of the kind shown in the table would be highly exceptional, occurring about once in 1,250,000 times. Corneal involvement, as compared with other regions of the eye, appears therefore to increase the severity of these injuries.

b. Severity and the Nature of the Agent.

Clinical experience commonly indicates that burns of the eye

caused by certain caustic alkalis tend to run a more protracted course than acid burns of similar degree. Evidence in support of this might be revealed by an analysis of severity in relation to the nature of the injury. It must be remembered, however, that the assessment of severity as defined earlier, depends on the number of days of attendance at hospital for treatment and not on the total duration of the injury. While a positive result would be of interest in answer to such a question, the absence of evidence of association between severity and acidity-basicity based on the data contained in Table 45 cannot be taken to preclude the possibility of such as association. The observations in the final two columns of the table are too sparse for analysis, so the discussion will be limited to the chemical and thermal classes of agent. Each of these classes has been further subdivided into three sub-classes, and the observations have been re-grouped for testing into fourfold tables to which Fisher's exact method has been applied. The results provide no evidence of association between the classifications presented in Tables 46 - 48 (B). Severity, assessed by this method, does not appear to bear any relation to the chemical or thermal nature of the injuring agent; within the chemical group acidity-basicity and miscellaneous chemical properties do not show any influence on severity; nor is there is any evidence of association between the physical states of the thermal agents and the severity.

c. Severity and Visual Acuity. From the data available the cases may be divided according to whether

the vision was known to be adequate or defective, in the terms already defined, before the accident occurred. The relevant observations are shown in Tables 49 and 50, and it has been calculated by the exact method that P = 0.105, a value which indicates that there is no evidence in the data of a relationship between the state of the visual acuity before the accident and the severity of the resulting injury.

(4) Localization in relation to Other Factors.

a. Localization and the Nature of the Agent.

Table 51 contains the observations with regard to laterality, but discussion is again limited to the chemical and thermal classes. Table 52 shows that there is no significant difference between these classes according to whether the right or the left eye has been affected. Considering the same classes, however, with relation to unilateral and bilateral injuries, a significant result is obtained when the χ^2 test is applied to the observations in Table 53. $\chi^2 = 4.808$; for n = 1, P = 0.028. This shows that some association exists between the classifications. The data in Table 53 do not reveal the nature of the association, but when the observations are re-arranged in Table 54, it is clear that the distribution with regard to laterality differs in the final row from that obtaining in the other rows. It appears that the vapour state tends to favour the production of bilateral injuries. To test this impression the cases in the chemical and thermal classes have been combined and re-classified according to the physical state of the agent, in Table 55. Considering solids and liquids

in Table 56, the exact method reveals no association with laterality; these two groups may then be combined and taken together in comparison with vapours as in Table 57. A value of 0.013 is obtained for P by the exact method. The observations show that the vapour state tends to favour the production of bilateral lesions, the solids and liquid states unilateral.

It is of interest to recall at this point that in the first analysis of the whole series of cases with regard to the laterality of the injuries, observed frequencies were found to be in very close agreement with the frequencies expected on the hypothesis that either eye of a pair had an equal chance of being injured and that the laterality was due to chance alone. But since the above results show that laterality is not due to chance alone but is associated with the physical state of the injuring agent, no inference with regard to the random character of the sample should be drawn from the laterality ratio.

The data in Tables 58 - 59(B) provide no evidence of any close association between the nature of the agent and the region affected.

b. Localization and Visual Acuity. Considering localization in relation to visual acuity, the data are insufficient to show whether in cases having defective vision prior to the accident, the laterality of the visual defect had any influence on the laterality of the lesion resulting from the accident. It can be determined, however, whether there is any evidence of association

between visual acuity and unilateral or bilateral lesions. The data are contained in Tables 60 and 61. The χ^2 test with Yates' correction gives a probability value about 0.78, showing that the classifications are independent.

In the same way the results obtained from Tables 62 - 64 show that there is no evidence in the data of an association between the state of visual acuity before the accident and the region of the eye affected, which is in accordance with expectation.

(5) The Nature of the Agent in relation to Visual Acuity.

It would not be expected that any relationship would exist between the nature of the agent and the state of visual acuity prior to the accident. This has been tested in the case of chemical and thermal agents with the data shown in Tables 65 (A) and (B) and the results are in accordance with expectation.

5. Analysis of Cases of Ocular Complication of Burns.- Group II.

This group consists of 7 cases; they are arranged in three classes according to the nature of the agent which was originally responsible for the condition.

A. Conditions due to Chemical Agent.

a. Late effects of mustard gas injury of the eyes..... 4

b. Ocular effects of systemic absorption of small quantities of chemical over a long period..... 1

B. Condition due to a Thermal Agent.

Metastatic endophthalmitis arising from septic burns of the trunk and limbs, caused by flame..... 1

C. Condition due to a Radiational Agent.

·Degeneration of ocular tissues and adnexa following X-ray therapy for carcinoma of the ethmoid sinus..... 1

A. Conditions due to a Chemical Agent.

a. Late effects of mustard gas injury of the eyes. It is now well known that in certain cases of mustard gas injury of the eye, the primary acute phase may be followed some years later by a characteristic type of corneal degeneration. Table 1 includes 4 cases of this kind; the records of these cases are worth detailed inspection and comment.

J.S.(Serial No. 96) Exposure to mustard gas occurred in 1917; no details are available to indicate the severity of the primary injury. He attended hospital first in 1937 complaining of defective vision in the right eye; the visual defect was found to be due to early senile cataract in this eye. Some conjunctival hyperaemia was present and the opinion was recorded that this was probably the result of a mustard gas burn. The absence of any corneal involvement was also noted.

This case shows a vascular disturbance present in the conjunctiva twenty years after an injury by mustard gas. The record is lacking in detail, however, and the opinion of the observer that the condition was the result of a mustard gas injury must be accepted.

A.McD.(Serial No. 95). This patient was first seen in 1937 complaining of defective vision in the right eye; he was known to have syphilis. He gave a history of mustard gas injury to the right eye sustained in 1917, but again details

of the severity of the original injury are wanting. Degenerative changes were found in the conjunctival areas exposed between the lids; the interpalpebral area of the cornea was occupied by a vascular scar. The opinion was recorded that the visual defect was due to the corneal condition, and that this was the result of exposure to mustard gas in 1917.

It is unfortunate that a detailed description of the lesion is lacking; the observed facts are consistent with a diagnosis of late degenerative changes in the cornea and conjunctiva due to injury by mustard gas twenty years previously.

H.Y.(serial No. 94) Detailed notes are available in this case. The patient was exposed to mustard gas in 1918 while acting as a stretcher bearer in the open. The eyes were bandaged for at least six weeks and he was detained in hospital for about a year. When first seen in 1943, the eyes were noted to be white and the cornea of each eye was anaesthetic. Characteristic scarring of the interpalpebral conjunctiva was present in both eyes: the right cornea was thin in places and contained diffuse irregular opacities, while the left had a central nebular scar with adherent iris. The condition of the left eye was explained when further questioning revealed that an ulcer had developed in this eye in 1940 which led to perforation. Slit lamp examination showed some interesting features. Variation in calibre of some of the small conjunctival vessels was noted but it was stressed that the number of new vessels observed in the conjunctivae of both eyes was remarkably few. Scattered

pigment spots were observed in the outer interpalpebral triangles. The right cornea was almost normal in the upper third, but in the lower two-thirds thickening and thinning was observed in various sections. Here again it was noted that there was very little vascularization and that there was no evidence of disused blood channels in the cornea. The anterior chamber appeared normal; the pupil was active and the iris structure was normal. The intra-ocular picture in the left eye was complicated on account of the perforation.

This patient's history is consistent with severe exposure to mustard gas in 1918. Twenty-five years later degenerative changes were present in the cornea and conjunctiva. It is of great interest that the relative absence of new vessels in the tissues was found worthy of comment by the observer and, in particular, that there were no deformed vessels or disused channels in the cornea. A.McW.(Serial No. 92). This patient's case was recorded in great detail; I was also fortunate in being able to examine him in 1946. In 1918 he was in a room of a partly demolished house in an area which was bombarded by gas shells for several hours. At dawn he lay down to sleep in contaminated clothing with others of his party. A little later he became hoarse, began to cough, became dyspnoeic, vomited and his eyes closed so that he had to be led to the Field Ambulance. He lost consciousness there for several hours and awoke to find himself in a hospital further down the line. The lesions at this time were stated to affect

both eyes, the chest and the skin of the left leg and scrotum. For 14 days he thought he was blind; then he discovered he could see by holding the lids open. By the 28th. day he could open his eyes slightly by looking down while wearing a forehead shade and at the end of the second month vision was stated to have become about normal. By the end of six months the skin burns had healed, the eyes felt normal, the chest condition had improved considerably, but the voice was still hoarse and it has remained so. Apart from this persistent hoarseness and slight chest trouble, he continued well for 21 years. In 1940 a dystrophic process began to develop in the central part of the exposed area of the right cornea; the left cornea was normal in appearance at that time. in 1942 there was an exacerbation of the chest condition with recurrent attacks of haemoptysis; repeated investigation for tuberculosis proved negative. By 1945 the corneal dystrophy had progressed in the right eye and was noted to have begun in the left.

The features of the ocular lesions are interesting. When first seen in 1940, 21 years after exposure to mustard gas, the patient complained of inflammation of the lids and deterioration of vision in the right eye. There were multiple white masses in the superficial layers of the central part of the interpalpebral area of the right cornea. The left cornea appeared normal except for a faint nebula in the upper temporal quadrant. There was no evidence of vascularization of either cornea and there were no cicatricial changes in the conjunctiva of either eye.

By 1945, there were map-like patches of uniform opacity in the superficial layers of the exposed area of the right cornea. A small area from which the opaque tissue had been excised for biopsy remained as a clear transparent facet. The central exposed area of the left cornea showed small round opaque dots and a cloudy opacity of the surrounding tissue. The surface was not elevated over these opacities. Careful slit-lamp examination showed no corneal vascularization, nor was there any sign of scarring in the conjunctiva.

To consider the differential diagnosis from other known types of axial degeneration in the cornea, it is clear that the clinical course was not that of senile epithelial dystrophy of Fuchs nor was there any evidence of endothelial change. The appearances resembled those of band-shaped dystrophy but it is rare for this condition to begin centrally in the cornea; moreover the patient was comparatively young and the condition appeared to be rapidly progressive. The lesion did not resemble the known types of nodular or reticular dystrophy such as those of Groenouw or Biber; the age of onset was late for this type of dystrophy and there was no evidence of a familial or a hereditary factor. Salzmann's type of corneal degeneration is preceded by phlyctenular keratitis and is not usually bilateral; previous phlyctenular disease could be excluded in the case of the left eye. Other types of corneal degenerative change such as vortex-shaped dystrophy were excluded by the appearance of the lesions.

In relation to the diagnosis of a late effect of mustard gas, the following points should be considered.

There was no clinical evidence of involvement of the conjunctival and episcleral tissues, and there was no trace of corneal vascularization. On the other hand, the onset many years after a severe mustard gas injury, the depth and position of the lesions in the cornea and their relatively rapid progress are factors which taken in combination with such general features of mustard gas poisoning as persistent hoarseness and chronic chest trouble, strongly support the diagnosis. It is known that experimentally produced mustard gas lesions of the cornea may undergo avascular healing (Mann and Pullinger 1942) but late corneal degeneration has not been observed in those cases. Again it is held by some observers (Mann and Pullinger 1942) that the late corneal degeneration of mustard gas injuries depends on invasion of the cornea by new blood vessels of abnormal form and their subsequent retrogression followed by cholesterin and fatty degeneration in the corneal tissue. If it is true that the invading new vessels in corneal disease never completely disappear (Duke-Elder, 1938) then it must be assumed that in this particular case avascular healing occurred after the primary injury in 1918. This raises the question of whether the presence of abnormal corneal vessels is a necessary and causative feature of the late corneal degeneration of mustard gas or merely a frequent concomitant and perhaps an aggravating factor.

b. Ocular effects of long-term systemic absorption of chemicals. Long-term exposure to noxious chemical substances may result in poisoning by systemic absorption.

This is an important aspect in industrial medicine; but only one case of this kind was referred for examination on account of possible ocular effects.

R.N. (Serial No. 88). This patient was a munitions worker engaged in handling tetryl (tetra-nitro-methyl-aniline) and lead azide. He complained of headaches and blood-shot eyes, of some five weeks duration. The refractive state was that of simple myopia in the right eye and mixed astigmatism in the left eye. There was congestion of the true palpebral conjunctiva of the lower lids, while the upper lids were normal. The corneae were of normal appearance and ophthalmoscopic examination revealed no abnormality in fundi or media.

The site and localized nature of the conjunctival injection in this case suggest that the ocular effect may have been due to an irritant reaching the conjunctival sac from the atmosphere rather than as a result of systemic absorption of chemical substances.

B. Condition due to a Thermal Agent.

Metastatic endophthalmitis arising from septic burns of the trunk and limbs, caused by flame.

A.McC.(Serial No. 1.) This patient was admitted to hospital in a severely shocked condition suffering from burns of the thighs, buttocks, and right forearm; her clothes had become ignited while she was kindling a fire. On the 6th. day after admission the left eye became markedly congested and there was slight mucoid discharge from the conjunctiva. The left pupil was widely dilated and fixed;

the aqueous was turbid and the fundus could not be seen. A pure culture of B. pyocyaneus was obtained from the blood. The patient died on the 7th. day.

Metastatic endophthalmitis is not a common condition and as a rule the ocular inflammation is only an incident in a very serious illness which usually ends fatally. It is possible that this condition may come under observation more often in the future as a result of the altered prognosis regarding the survival of septicaemic cases which has been brought about by penicillin treatment. The particular organism responsible in this case is very unusual as a cause of metastatic endophthalmitis.

C. Condition due to a Radiational Agent.

Degeneration of ocular tissues and adnexa following X-ray therapy for carcinoma of the ethmoid sinus. W.J.(Serial No. 4). This patient, aged 8 years, was treated by X-ray therapy for malignant disease of the right ethmoid sinus. Very large doses were given during the year 1935. In February 1936 it was noted that there was superficial excoriation of the lower part of the right cornea. Later an abscess developed in front of the right lachrymal sac and this was followed by obstruction of the lachrymal passages on the same side. In February 1937 there was atrophy of the skin of the right side of the nose and the skin of the eyelids was also affected with loss of the eyelashes on that side. Telangiectases were present in the skin. In the right eye there was some varicosity of the conjunctival vessels. In the lower part of the cornea a

a nebular opacity was observed and there was marginal vascularization in the upper part. The lens and fundus were normal in appearance. By September 1937 a cluster of white spots had appeared in the posterior lens cortex and vision was considerably reduced. In March 1939 delicate lens opacities were noted in the subcapsular zone anteriorly in addition to the coarser opacities already noted posteriorly. There was a patch of atrophy in the iris. During the next few days vascularization extended further into the cornea and vision progressively deteriorated until in March 1945 the eye became blind and painful with a raised intraocular tension and was excised.

This case shows several interesting features. In the first place, there was a latent period of several months before any signs of tissue degeneration appeared. The first changes were observed in the corneal epithelium; the commencement of corneal vascularization was noted a year later. The first changes in the lens appeared about two years after the last treatment by X-rays. Changes in the uveal tissue did not appear for four years. The degenerative changes appear to have beeh of a progressive nature.

6. Ocular Effects of Accidental Exposure to Mustard Gas Vapour.

A unit of soldiers moved into new billets in 1943. One of the party found a tin of dark liquid in the basement and decidedto repaint the grates, thinking that the tin contained lacquer, when in fact it contained mustard gas

liquid. With the help of two others the liquid was applied by brush to the grates and surrounding ironwork of the open fireplaces in eight bedrooms. Later that day fires were lighted and at night, the men of the unit, after closing the black-out shutters, lay down to sleep. The eyes were affected by mustard gas vapour in twenty-five cases. Detailed ophthalmoscopical examination was made in all cases and several of the men were observed over a period in hospital. With regard to the ocular lesions alone it was found that the cases could be classified into three groups.

Group I. Very mild cases. Conjunctiva hyperaemic. Cornea not affected. Vision not affected. Fit for duty within a week.

Group II. Mild Cases. Conjunctiva hyperaemic, and injury to corneal epithelium only. No permanent impairment of vision. Fit for duty in three weeks.

Group III. More severe cases. More serious injury to conjunctiva and cornea. A varying degree of visual impairment may result in a small proportion. Fit for duty on an average in three months.

It was noted that a small proportion of cases apparently in Group II might later be found to be Group III cases, and that Group III included cases which might relapse years later. The complete data are shown in Table 66.

The distribution of cases within these groups was as follows:-

Group I. 14 cases.

Group II. 9 cases.

Group III. 2 cases.

The range of severity of the ocular lesions is

consistent with experience of mustard gas vapour effects, and differences in severity are probably due to factors such as variation in vapour concentration in different rooms, or in the distance of the mens' beds from the contaminated fireplace in the case of a group of men from the same room. It is also wellknown that considerable individual variation in sensitivity to mustard gas may be found amongst a group of persons exposed to the same concentration of gas.

One case (No. 2). showed corneal bedewing without any signs of conjunctival involvement, while in two cases (No. 7 and 9) oedema of the corneal epithelium was found in the presence of only slight conjunctival involvement. Triangular areas of pallor in the interpalpebral zone of the conjunctiva were observed in one patient only (No. 11) and elsewhere it was noted that this case appeared to be the worst from the point of view of ocular effects. Corneal vascularization did not occur although the most severely affected cases were observed over a period of seven weeks.

Corneal staining with fluorescein was observed in two cases only (No. 5 and 6) on the fifth day, and in one was still present on the ninth day. The case thought to be most severely affected has no record of the presence of corneal staining. These facts are consistent with experimental experiences, in that there appears to be relatively little tendency to epithelial cell necrosis and desquamation following exposure to mustard gas as compared with similar exposure to certain other chemical substances. It should also be noted that transient epithelial staining

may have occurred on the third or fourth day.

The data are incomplete, unfortunately, with regard to the laterality of the effects and it would be unsafe to draw conclusions from them with regard to this feature.

On consideration of the collateral evidence of the effects of mustard gas apart from the ocular lesions, some indication of the severity of the exposure is given by the fact that there is no record of any patient having vomited following exposure. This suggests that the degree of exposure was relatively mild. A complaint of sore throat is noted in several cases and other manifestations such as skin erythema, oedema of the skin of the lids, and blisters were observed.

The grouping of cases with regard to severity, and the frequency distribution within the groups is consistent with other experience of such lesions. With due regard to the cautionary note that Group II cases may relapse it is probable that the general conclusion that none of these cases was likely to result in late corneal degeneration is well founded. This group of cases illustrates clearly that while the ocular effects of mustard gas vapour may cause much discomfort and short-term harassment, it is only in a very small proportion of such cases that there is any risk of permanent ocular damage.

PART 1.

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PART 2.

"This Analysis consists in making Experiments and Observations and in drawing general Conclusions from them by Induction, and admitting of no Objections against the Conclusions, but such as are taken from Experiments, or other certain Truths....."

Sir Isaac Newton, Opticks, 1730.

PART 2.

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PART 2.

THE EFFECTS OF CERTAIN CHEMICAL SUBSTANCES ON THE EYES OF EXPERIMENTAL ANIMALS AND OF MAN.

1. The Nature of the Study: its scope and limitations.

The work described in this part was mainly directed towards the preliminary assessment of the ocular effects produced by new chemical warfare agents. Observations were made both in the laboratory and in the field. The investigation was often necessarily incomplete. It was not possible to pursue a course of purely scientific interest while an urgency existed to make a preliminary assessment of new substances. Further, a substance causing a severe reaction in the eye might prove to be of little interest as a war gas on account of physical or chemical properties which precluded its use in the field. Limitations of this kind were compensated, however, by the diversity of problems and by the wider experience obtained through the study of many different chemical compounds.

Several species of animals were available for preliminary experiments but it was sometimes necessary, in the final stages of an investigation, to determine directly the dosage required to produce threshold effects in the human eye. Most of the work was carried out with simple equipment fashioned in the laboratory. Routine clinical examinations were made by lens and loupe, while there were facilities for more detailed study under the slit-lamp. Gross pathological changes were observed by means of the dissecting microscope, and, in selected cases, sections of the injured tissues were

obtained for histological examination.

It is proposed to describe the work broadly, from both the experimental and ophthalmological aspects. The errors and difficulties arising from the experimental approach have been included as well as the characteristic clinical and pathological features of the resulting lesions.

2. The Test Substance.

The substances examined were of two types; those considered to be capable of causing injury to the eye, and others thought to be potentially useful in therapeutics or as antidotes.

(1) Chemical Properties.

The chemical properties of the test substance must be reviewed. They may be well known or may have to be inferred, in the first instance, by analogy with other better known compounds of the same group. These properties may be of importance on account of the interactions which take place in the tissues, and since the reactivity of the substance may be a source of experimental error. The tendency of a substance to undergo hydrolysis may be of great importance.

(2) Physical Properties.

It is important to make observations on the physical state of the substance at atmospheric temperature and pressure, and to know such characteristics as vapour pressure, freezing point, reaction and solubility in the usual solvents.

(3) The Nature of the Hazard.

By considering such chemical and physical

characteristics as have been indicated above together with observations on the presence of an odour or sensory irritant properties, it is possible to make an assessment of the nature of the hazard to the eye which is likely to arise from the use of a particular substance in industry or in war. The eye may be affected insidiously by exposure to toxic vapours, or suddenly by a splash of irritant liquid. This differentiation is important with regard to problems of therapy.

3. The Experimental Subject: choice of species of animal.

Many factors are involved in selecting a particular species of animal for purposes of experiment. For instance, clinical examination of the eyes of rats and mice is extremely difficult on account of the small size of the eyes; the animals are also difficult to control during examination. By comparison the eye of the horse is large and easily accessible, but this species can only be used for special purposes since it is neither available nor economic for study in large numbers. The eye of the pig is often held to bear close resemblance to the human eye with regard to size, texture and sensitivity, but even under conditions of plenty it is not economic to use a large series of live pigs for experimental purposes. Goats are readily available, but the resistance of the goat's eye to chemical injury appears to be of a low order and the course of the lesion is difficult to follow since, in some cases, the eye tends to proceed rapidly to destruction. On the other hand, the goat's eye was found to be a very sensitive index of contamination in field trials. The dog, the cat and the monkey were available in limited numbers and

are species suitable for experiments on a small scale. As regards common sensation, some observers are of the opinion that the eye of the dog most closely resembles the human eye. With regard to most features, however, the eye of the monkey is usually considered to bear the closest relationship to its human counterpart, but I was not able to form an opinion on this matter as the number of experiments in which monkeys were used was too few. The rabbit is readily available, easily handled, and is very amenable to ocular examination even by slit-lamp. The eye of the rabbit is accessible and of convenient dimensions for clinical study; albino animals can be obtained readily for special purposes. As a rule, therefore, the rabbit was the animal of choice in the early stages of an investigation. It must be stressed, however, that it would be unsafe to extrapolate results obtained on the eyes of one species of animal only as a final opinion in terms of the human eye.

4. Experimental Methods.

(1) General Considerations.

a. Planning.

The aim of the experiment should be formulated clearly, and the design must be carefully planned. Having reviewed the physical and chemical properties of the test substance, and having assessed the nature of the hazard to the eye, a trial may be made to determine whether a common and easily available species of animal will give a suitable ocular lesion. Consideration should be given to factors such as age, sex and weight in selecting the individual

animals. It is desirable to obtain uniformity between the animals which are to be compared, but if the contra-lateral eye is to be used as a control then stringent uniformity from one animal to another with regard to breeding, age, sex etc., is not essential. The nature of the hazard to the eye will indicate the physical state and dosage in which the chemical substance should be applied to the eye, and an attempt should be made to foresee the sources which may contribute to the errors of the experiment. Finally, the method of assessment of the lesions must be considered, the duration of the experiment decided, and a suitable programme of clinical examination planned.

b. The Ideal Experimental Lesion.

The conditions to be desired in the production of an ideal experimental lesion of the eye may be stated as follows:-

1. The quantity of the agent used to produce the lesion should be accurately measured, and all lesions which are to be compared should be produced by similar accurately measured quantities of the agent.

2. If the agent must be exhibited in a vehicle, the vehicle should be bland, and the agent should be distributed evenly throughout the vehicle. Identical samples of the vehicle should have an identical content of the agent. The agent should be stable in the vehicle or should be freshly prepared immediately before use.

3. The experimental conditions should simulate those expected to occur in the human eye exposed to the agent. Blinking should be simulated by momentary closure of

of the eyelids of an anaesthetised animal after a lesion has been produced if this would be the expected reaction to the agent introduced without anaesthesia in the human.

4. In exhibiting any therapeutic substance or antidote, the bland vehicle or similar bland substance should be introduced into the control eye. Factors such as the reaction and the osmotic pressure should be taken into account.

c. Anaesthesia.

In these experiments general anaesthesia was produced by means of Nembutal given intra-venously or intra-peritoneally, the dosage being based on the number of kilograms of body weight of the animal.

d. Care of the Experimental Animals.

It is well known that social conditions may affect the health of the individual of the human species. For the same reason the investigator must ensure that the experimental animals live under suitable conditions and are properly fed and attended. The premises must be regularly cleaned and fresh bedding supplied; the matter of exercise should be given attention.

In the particular case of experiments on the eye, it is often necessary to keep animals singly since they tend to lick the affected parts of other animals occupying the same cage. On the other hand prolonged isolation may prove to be detrimental to the general well-being of the animal and may be contra-indicated. When an animal is in poor general condition this is often

associated with deterioration in the local eye condition.

(2) Exposure to Vapour.

The eyes of animals may be exposed to vapour by three main methods:-

a. The Static Chamber.

b. The Constant Flow Chamber.

c. Applicators.

a. The Static Chamber.

The chamber is of known capacity, 10 cubic metres or 100 cubic metres being useful sizes. Before beginning an experiment, dispersal of a cloud of visible smoke in the chamber will demonstrate any leaks which require to be sealed. The chamber is fitted with glass observation panels and should have an adequate number of channels cummunicating with the outer air for transmission of connecting wires and tubes; these channels must be rendered gas-tight before the experiment begins. In the static chamber the test substance may either be vaporised by means of heat or by spraying, and fans are required to ensure rapid and uniform dispersal of the vapour throughout the chamber. Samples of the atmosphere must be withdrawn for quantitative analysis at regular short intervals during the entire exposure as a guide to the rate of decay of the gas content, and in certain cases the atmosphere may need to be boosted by further addition of gas from time to time in order to maintain the concentration at a relatively constant level. The dosage is indicated approximately by the product of the concentration of gas (mg./cub.metre) and the duration of the exposure (min.), and is designated CT.

Certain technical details are important in investigating the effects of vapours on the eye. Precautions must be taken that the eyes are exposed throughout the whole experimental period, and to achieve this, sutures may be inserted in the eyelids in such a way as to hold the eyes open and to prevent the third lid from covering the cornea. In order to produce a moderately severe lesion in the eye, it may be necessary to use a dosage of vapour which would certainly cause serious respiratory and systemic effects by inhalation or by skin absorption. It is essential, therefore, to expose the head only, and to fit up a system of masks and breathing tubes connected to the outer air. It was found necessary to give each animal separate breathing apparatus in the case of exposures lasting about 30 minutes since the air in the tubes became vitiated when the animals were connected in series.

b. The Constant Flow Chamber.

Using the constant flow method the test substance is vaporised outside the chamber and the vapour is delivered into the chamber continuously during the experiment. The rate of delivery is controlled by means of a flowmeter.

c. Applicators.

Applicators have been devised which use either the static or the constant flow principle, and which make it possible to apply the vapour to the eyes alone.

(3) The Paraffin Solution Method.

Owing to the technical difficulties involved in chamber experiments, it was evident that the investigation of

a large number of substances by these methods would be very tedious, and that some simple technique was required for the production of a reproducible vapour-type lesion. Robson and Scott (1941) had shown that accurately measured quantities of a 1% w/v solution of liquid mustard gas in liquid paraffin produced lesions in the eye which were similar to those caused by moderately severe exposure to mustard gas vapour, which were reproducible with sufficient uniformity, and which were very simple to produce.

Liquid paraffin consists of a mixture of hydrocarbons and is highly purified when intended for medicinal use; the name paraffin is derived from the chemical inactivity of this group of substances. Amongst approximately fifty substances tested, there was only one case in which paraffin was unsuitable as a solvent in that the test substance was not miscible with liquid paraffin in the proportion of 1% w/v to give a clear solution.

It was found by comparison with chamber experiments that the paraffin solution method produced ocular lesions of vapour type using several different test substances. The solution was delivered from a pipette calibrated at room temperature to contain 0.025 c.c. of Liquid Paraffin.B.P. The drop was allowed to fall from the pipette to the limbus at the position of 12 o'clock and from there to run over the cornea. The actual size of drop delivered was estimated to be about 0.015 c.c. This dosage of mustard gas and nitrogen mustard gas solutions was found to correspond to exposures to the undiluted vapours of the order of CT = 7500.

(4) Exposure to Liquids and Solids.

The hazard to the eye from solid chemical substances is not of importance in warfare; particular features associated with the solid state will be mentioned in the following pages. On the other hand, the effects of chemical substances in the liquid phase, being of considerably greater importance, were studied over a wide range of drop sizes. In the initial cloud produced by explosion, the droplets are of the order of 30 - 200μ in diameter. Under field or factory conditions the cloud may consist of earthy particles impregnated with liquid chemical. Particles of dry appearance can hold drops of liquid up to about 30 μ in diameter.

a. The Wind Tunnel.

It was found possible to release a spray of fine droplets at a known wind speed in the experimental wind tunnel. The coarsest spray which it was practicable to use in the tunnel gave a rather finer cloud than was produced under field conditions. It was found by means of a sampling device that the largest drops were of the order of 90μ in diameter, while 50% of the mass was delivered in drops of about 37μ in diameter.

The ocular effects of small drops and solid particles can be studied by this method. An estimate can be made of the area dosage to which the eye is exposed, and is expressed in mg./sq.m. This may be converted into terms of CT by the formula:-

Area dose (mg./sq.m.) =

CT (min.mg./cub.m.) X Wind velocity (m./min.)

b. The Microburette.

Drops ranging upwards from about 150 μ in diameter can be obtained by means of this instrument. A steady current of air is directed to impinge on the fluid emerging from the bevelled portion of a needle attached to a burette. The fluid is blown off in small droplets of equal size at a steady rate. A count is made to determine the number of drops given by a measured volume of fluid, from which the drop size may be estimated. Having adjusted the instrument to give the desired size of drop, the requisite number of drops may be directed into the eye of an anaesthetised animal.

c. The Microsyringe.

Larger drops can be delivered by the microsyringe. This instrument has a micrometer screw gauge connected to the piston, and by turning the gauge a small measured quantity of fluid is ejected on to the bevelled surface of the needle attached to the syringe. This bevelled portion is then laid carefully on the surface of the eye. Drops of the order of 0.0002 c.c. and upwards can be obtained by this method.

d. The Calibrated Pipette.

This is a glass tube of small bore with a flat end from which a drop is allowed to fall by the action of gravity. It is known that when a drop falls by gravity from a vertical tube, the suspended drop becomes unstable before it leaves the end of the tube, and a constricted

portion develops in the fluid connecting the drop to the tube. The main drop separates at the lower end of the constricted portion which later also separates as an additional small drop. Both the large and small drops must be taken together as one drop. It is also known that the weight of such a drop depends on the radius of the circle forming the outer limit of the end of the tube amongst other factors. (Stuhlman, 1943).

Calibrated pipettes were used to give drops of the order of 1 mm. in diameter.

5. The Sources of Error.

It is essential in any experiment to consider the probable sources of error, and, if possible, to estimate the amount of error. The errors which arose in these investigations may be discussed conveniently under four headings:-

(1) Errors associated with the test substance.
(2) Errors associated with the experimental methods.
(3) Errors associated with the experimental subject.
(4) Errors associated with the observer.

(1) Errors associated with the Test Substances.

Different methods of production of a chemical substance may be responsible for variations in activity between different samples. For instance, an impression was formed that small quantities of a particular substance prepared by laboratory methods were more active in the eye than samples of the same substance prepared in bulk by industrial processes.

It is also conceivable that alterations in

activity may result from interaction between a chemical substance and the container in which it is stored, or that extreme variations in temperature occurring during prolonged storage might affect the activity of the sample. These factors did not have a significant effect on the activity in the few instances in which they were investigated.

Certain substances readily undergo hydrolysis in the presence of water. In some instances the different products of hydrolysis showed a wide range of variation with regard to their activity in the eye.

Errors may also arise in the quantitative estimation of vapour concentrations by chemical methods in the early stages of an investigation when the behaviour of the vapour is not fully known.

(2) Errors associated with the Experimental Methods.

a. Vapour Methods.

The technical difficulties associated with the establishment and maintainance of vapour concentrations in a gas chamber are numerous.

The method of dispersal may affect the concentration. In some experiments it was found that when heat was used to vaporise a substance the resulting concentrations were considerably below theoretical expectation, and that more consistent results were obtained by spraying. The distribution of a gas throughout a static chamber may lack uniformity unless the atmosphere is thoroughly mixed by fans. Loss of vapour by leakage has already been mentioned.

The condition of the atmosphere with

regard to temperature and humidity may be responsible for variations in vapour concentration. During an experiment there may be a sudden increase in the humidity within the chamber if micturition occurs amongst the animals. If the chamber is of small capacity and if the test substance is readily hydrolysed the resulting variation in concentration may be sufficient to invalidate the experiment.

Vapours differ in their tendency to undergo surface adsorption. This tendency may be increased by certain materials amongst the apparatus in contact with the gas and may accelerate the rate of decay of the vapour concentration.

The duration of the experiment has an important bearing on the gas concentration in static chamber experiments. It is exceedingly difficult to maintain a relatively constant concentration of vapour over a considerable period of time, and the difficulty is greater the lower the concentration and the longer the duration. This difficulty applies more to the static method, but in an experiment to determine the effects of long exposure to low concentrations of vapour using a small chamber by the constant flow method, the error with regard to dosage was so great that the investigation had to be abandoned.

It has already been mentioned that measures may have to be taken to control the eyelids and to avoid systemic poisoning when using gas chambers to produce vapour effects on the eyes.

Local applicators have been used by some investigators to produce vapour lesions of the eye. The

difficulty associated with the estimation of dosage is, in my opinion, a serious disadvantage in the use of such apparatus.

b. Paraffin Solution Method.

While it would be unsafe to accept as a generalization that the ocular effects of an agent dissolved in liquid paraffin are necessarily similar to those of the same substance presented to the eye in the form of vapour, it would be expedient if it could be shown that (a) the substance was soluble in liquid paraffin, and (b) that the paraffin solution did, in fact, reproduce all the features of the ocular lesion resulting from exposure to high CT values of the vapour. Once these points have been cleared up, relatively uniform and reproducible lesions can be obtained by the paraffin solution method at a stage when the behaviour of a little known substance may be unpredictable in the gas chamber. The method was used in experiments involving about 50 different compounds, and errors associated with the chemical or physical properties of the solutions were not considered significant.

It was found, however, that the ocular lesions varied in severity according to the grade of paraffin with regard to viscosity and density, lighter and less viscous paraffins producing less severe lesions. The lesions were most uniform when the solutions were made with Paraffinum Liquidum B.P., having a kinematic viscosity not less than 64 centistokes at 37.8° and density of 0.880 - 0.895 at 15.5°. Factors such as viscosity and density will

affect the size of drop delivered from a pipette, and may influence the period during which the solution remains in the conjunctival sac before it is removed mechanically with the tears.

The actual variation in weight of the drop of Liquid Paraffin B.P. delivered by a pipette calibrated to contain 0.025 c.c., was found by experiment to be of the order of ± 5%.

c. Liquid Methods.

In the wind tunnel the dosage which enters the eye is estimated by repeating the experiment under identical conditions using a droplet sampling device in place of the eye. A very accurate estimate of dosage can be made in microburette experiments; the most likely source of error lies in the counting of the drops as they enter the eye. In the case of the microsyringe, however, errors of dosage are very liable to occur. This may be due in part to the physical properties of the test substance and in part to a personal factor, since the technique of the method involves the touching down of a drop of the test substance on to the surface of the eye. In falling drop methods errors may arise from the physical factors already mentioned or from the technique of delivery of the drop.

(3) Errors associated with the Experimental Subject.

a. Individual Variation.

The existence of individual variation in the biological response to drugs is well known, and similar variation is found in the ocular response to chemical injury. When a relatively constant dose of the same chemical

substance is applied to the eyes of a series of animals of the same species it is seen that individual variation must be taken into account amongst the sources of experimental error. The amount of scatter varies with the substance used; it is greater with arsenical substances than with mustard gas.

The error due to individual variation may be reduced by using inbred stock of uniform age, weight and sex, and by including a sufficient number of animals in the series. Moreover, since the eye is a paired organ, the effect of the variation may be offset by using the contralateral eye of the same animal as a control. In some cases a standard substance whose action in the eye was well known was applied to the contralateral eye for comparison with the test substance.

In experiments using liquid contamination Scholz (1943) found that the difference between the reactions of the two eyes of an animal was less than the combined errors of assessment and dosage. In the course of my work an impression was gained that when the substance applied to one eye had a severe effect, the response to the compound applied to the contralateral eye was enhanced.

The severity of the ocular reaction may vary with the general health of the animal, or with the presence of local eye disease.

b. Species Variation.

(a) Anatomical Variation.

The anatomical features of the anterior segment of the human eye are familiar. The eyes of other vertebrates correspond to the same general pattern

but some variations in structure occur from species to species.

The Anterior Layers of the Cornea.

The Epithelium:- The number of cell layers forming the corneal epithelium varies considerably in different species, (Fig. 1 - 6), from about 4 in the rabbit to about 20 in the horse. In most species the epithelium at the limbus contains melanin pigment in its deeper cell layers, illustrated in the rabbit in Fig. 13. This pigmentation is not found in the human amongst white races.

Bowman's Membrane:- This structure reaches its greatest development in the human eye (Fig. 1); it is rudimentary in the monkey (Fig. 3). Bowman's membrane cannot be identified at all in the rabbit, dog, goat or horse (Figs. 2, 4, 5 and 6), although when the cornea has been denuded of epithelium, a well defined basement membrane may be seen in these species.

The Posterior Layers of the Cornea.

Descemet's Membrane:- A homogeneous layer corresponding to Descemet's membrane was found in all the species examined. Its appearance in the rabbit, the dog and the goat (Figs. 8, 10 and 11) closely resembles the appearance in the human eye (Fig.1). It is remarkably well developed in the horse (Fig.12), whereas it is quite rudimentary in the monkey, (Fig.9).

The Endothelium:- This structure has similar histological appearances in different species, but the pattern revealed by slit-lamp examination of the zone of specular reflection in the rabbit differs from that seen in man.

The Cornee-scleral Junction.

Although pigmentation was present in the epithelium at the limbus in all the species examined, considerable variation was observed from species to species in the amount of pigment distributed throughout the sclera at the corneo-scleral junction. Numerous chromatophores were found at all levels in the dog (Fig.17) and pigment was also present in this region in the goat (Fig. 18), but in the human eye (Fig. 15), as well as in the monkey, the rabbit and the horse (Figs. 16, 19 and 20) pigmentation of the sclera was not a feature. Pigment-bearing cells were not observed normally in any species within the substantia propria of the cornea.

The Angle of the Anterior Chamber.

It is not uncommon in the normal rabbit to find an attachment between the periphery of the iris and Descemet's membrane in the angle of the anterior chamber (Fig. 19). A similar condition was observed in the horse(Fig. 20). In this species Descemet's membrane is a broad band and may appear to split with inclusion of the iris tissue near the angle in the vicinity of adhesions of this kind. Such iris attachments were not observed in normal eyes of other species examined.

The Ciliary Body.

The ciliary body is a well-developed muscular organ in man and in the monkey (Figs. 15 and 16); the trabecular portion adjoining the angle is relatively small. The processes are of simple pattern and arise from the ciliary

body only. In the other species illustrated in Figs. 17 - 20, the trabecular structure is relatively more prominent and muscle fibres are scanty; the pattern of the processes may be complex as in the horse(Fig. 22), or simple as in the rabbit(Fig.21), where they take origin from the back of the iris as well as from the ciliary body.

The Iris.

Considerable variation is found in the texture of the iris stroma. It is delicate in the human, the monkey and the rabbit (Figs. 23, 25 and 24), and is dense and collagenous in the dog, the goat and the horse (Figs. 26, 27 and 28). Crypts are formed by folding of the anterior surface in the horse(Fig.28). Considerable differences are also found in the number and shape of the chromatophores. In the monkey and in the dog (Figs. 25 and 26), these pigment-bearing cells have the appearance of broken twigs; they are abundantly present in these species and in the horse (Fig. 28). Chromatophores are more scanty in man, in the rabbit and in the goat (Figs. 23, 24 and 27). In many animal species some degree of ectropion of the posterior pigmented layers of the iris may normally be found. This occurs in the horse, but here in addition, an accumulation of pigment cells may be observed projecting from the pupillary margin and having a vascular core of iris stroma. This constitutes a floccule and is a normal appearance in the horse (Fig. 14). The iris musculature is poorly developed in the goat as compared with other species examined. The major arterial circle lies in the anterior part of the ciliary body in the human, but in the

rabbit (Fig. 21) it is found in the base of the iris where it is easily seen on clinical examination in an albino animal.

(b) Physiological Variation.

Differences were also noted with regard to ocular physiology. Animals such as rabbits, guinea-pigs and cats, are undisturbed by high concentrations of lacrimatory vapour which cause complete incapacity in man through lacrimation and blepharospasm.

Marked differences in common sensitivity occur in the eyes of different species. The dog and the pig are said to resemble the human in corneal sensitivity, but it is not uncommon to find a large foreign body, such as a fragment of wood or a piece of straw, in the conjunctival sac of the rabbit while the conjunctiva remains pale and the animal does not seem to suffer any discomfort. The normal rabbit may show punctate staining of the corneal epithelium with fluorescein, visible macroscopically, yet the eye remains pale and quiet.

The rabbit often exposes the cornea without blinking for periods up to twenty minutes or so. The surface becomes dry and pitting may occur but this does not appear to cause any damage to the corneal tissue.

(c) Pharmacological and Pathological Variations.

If a drop of diethyl fluorophosphonate of about 1 mm. diameter is placed in the conjunctival sac of an average 2 kilo. rabbit it causes convulsions and death in

approximately half an hour. The same quantity of this substance, applied in the same way, causes severe convulsions in a rat of about a quarter of the rabbit's body weight, but the rat recovers completely in an hour or two. A guinea-pig of about half the rabbit's weight remains quite unaffected by an identical dose of this compound.

The cornea of a goat may slough a few days after an exposure to mustard gas vapour which does not result in loss of the eye in other species.

Pathological processes progress at different rates in different species. It was desired to produce a minimal ocular lesion in animals with certain vapours, a recoverable lesion of similar severity to welder's flash in the human eye. This was attempted in rabbits using mustard gas but had to be abandoned because, in addition to the errors involved in chemical sampling and in maintaining relatively low concentrations of vapour, the threshold lesion was too indefinite, on account of its extremely transient nature in the rabbit. Again, late corneal degeneration of mustard gas may take years to develop in the human but appears in rabbits after a period of months.

These examples indicate some of the factors which must be taken into account in extrapolating the ocular effects obtained in different species of animals in terms of the human eye.

(4) Errors associated with the Observer.

Integrity and self-criticism are

essential in the observer. Close attention to technical detail is necessary for producing uniform lesions. Unavoidable errors arise in any experiment but these may be kept at a minimum by adopting a definite technique and ensuring that the process is repeated in identical fashion on each occasion. For instance, the angle at which a pipette is held above the eye affects the weight of substance delivered by a falling drop method. It is also important that the drop should be allowed to fall and not be expelled by force in such a method.

The personal factor is of great importance in assessing the severity of the lesions. For this reason the method of assessment should be as objective as possible. If a collaborator is available much can be done to eliminate personal bias by arranging that the observer who makes the assessment shall not know the details of contamination, or that each observer shall make an independent assessment. It is a wise precaution to repeat the experiment several times.

From the brief survey of experimental errors given in the preceding sections it is evident that the sources of error in investigations of this kind are considerable. In addition to the errors arising from physical and chemical sources, a wide range of variation occurs in those ocular features which can be observed by relatively gross methods such as clinical or histological analysis. Conclusions from such experiments must only be drawn with caution and results must be obtained from

several species of animals before being extrapolated in terms of the human eye.

6. Methods of Examination, Assessment and Recording.

The aim of the experiment may influence the duration of the period of observation and the frequency of clinical examination. The animals should be observed while they are being exposed to vapour in the gas chamber for evidence of sensory irritation or increased conjunctival secretion. The time of onset of conjunctival congestion and oedema should be recorded. When using drops, the animal's behaviour may indicate whether the process of contamination is painful. The ocular condition should be assessed within the first few hours lest transient effects be missed, but thereafter clinical examination may be made at daily or longer intervals according to the indications.

Much information can be obtained by naked-eye inspection followed by detailed examination by lens and loupe. For purposes of examination small animals are most easily controlled by placing them on a towel in the sitting position. The towel is then wrapped tightly round them to control their movements and they are allowed to sit on a flat surface such as the laboratory bench. In this way they struggle less and appear to feel more secure than if they are held in an assistant's arms or placed in a box with the head projecting.

More minute study can be made by means of the slit-lamp and corneal microscope. The rabbit is easy to examine in this way. The forehead and chin

rests are removed from the instrument and replaced by a flat wooden platform on which the animal, secured in a towel, sits during the examination.

Larger animals or those which are more difficult to handle may have to be examined at less frequent intervals, or even only at critical stages in the course of the lesion under general anaesthesia.

It is useful to adopt a numerical method to assess the relative severity of different lesions of the eye. The features chosen must be capable of rough classification into different grades of severity. The total value for a particular lesion should give a numerical estimate of the clinical impression of the severity of the lesion relative to other similar lesions or to the same lesion on another day. The points on which the estimate is based need not contribute directly to the absolute severity of the lesion.

The following scheme was used to compare lesions of the anterior segment of the eye in the primary acute phase of the ocular response:-

	FEATURES.	MAXIMUM VALUES.
Lids:-		
	Oedema.	2
Conjunctiva:-		
	Congestion.	4
	Oedema.	4
	Desquamation.	4
	Haemorrhages.	4
	Discharge.	4
Cornea:-		
	Epithelial oedema.	4
	Intra-corneal changes (oedema and infiltration).	4
	Epithelial desquamation (staining with fluorescein).	4

	b/f	34
Iris and Anterior Chamber:-		
	Congestion and oedema.	4
	Haemorrhages.	4
	Functional abnormality.	4
	Exudate (hypopyon).	4
	Total.....	50.

Having assessed the lesions by a method of this kind the test substances can be arranged roughly into groups according to their activity in the eye:-

No Lesion.....	0
Slight.....	X
Moderate.....	XX
Severe.....	XXX
Very Severe.....	XXXX

The records may be supplemented by sketches or photographs of special features of the ocular condition. The dissecting microscope was used to confirm clinical findings in those cases in which a complete histological investigation could not be undertaken.

7. The Experimental Results.

The results may be discussed under three main headings.

A. Comparison of the Activities of different Chemical Substances in the Eye.

B. The Clinical Effects produced in the Eye by the action of Chemical Substances.

C. Therapeutic Measures in Chemical Injuries of the Eye.

A. Comparison of the Activities of different Chemical Substances in the Eye.

Since vesicant substances such as Lewisite and Mustard gas can produce structural damage if introduced into the eye, it was considered probable that other related

organic compounds might also cause eye injury. In a study of the effects of equal weights of certain test substances dissolved in Liquid Paraffin B.P. applied to the right eyes of a series of rabbits and compared with the same quantity of a standard substance (e.g. Lewisite or Mustard gas) applied to the left eyes of the same animals, a rough indication of the comparative severity of the resulting lesions was obtained. The compounds which were examined are arranged by chemical constitution in Table 67. The severity of the lesions is shown ranging from NO LESION.....0, to VERY SEVERE.....XXXX; where the activity is border-line between two groups brackets are used....XX(X).

The dosage on which these comparisons were made (0.025 c.c. of a 1% w/v solution in Liquid Paraffin B.P.) is considered to be roughly equivalent to a CT value of about 7500 min. mg./cub.m. in the case of mustard gas vapour. The results are thought to have particular reference to the vapour type of lesion, and it would be unsafe to draw conclusions from them with regard to the effects of a substance applied to the eye in liquid form.

It was observed in other experiments that substances having lacrimatory properties only in the vapour state, could produce structural damage in the eye when introduced in the form of liquid or in solution (e.g. Bromobenzyl cyanide and Chloracetophenone). Table 67 contains two substances, diphenyl chloroarsine and diphenyl cyanoarsine, which are best known for their nasal irritant

properties, although they also cause lacrimation. It appears that they are also capable of causing injury to the eye when applied in dosage of this relatively high order.

Amongst compounds which produced no structural damage in the eye were diethyl- and di-isopropyl fluorophosphonates, two substances having a potent miotic action. It will be recalled, however, that a drop of undiluted liquid diethyl fluorophosphonate of 1 mm. diameter instilled into the conjunctival sac was found to be lethal for a rabbit of average weight.

Mustard sulphone, the hydrolysis product of mustard gas, proved to be relatively inactive in the eye. In other experiments a study was made of the action in the eye of the hydrolysis products of ββdichlor diethyl methylamine. The parent substance has a characteristic effect, causing severe keratitis and iritis with gross intraocular haemorrhages. If dissolved in cold water and used immediately, the aqueous solution (1% w/v) produces a lesion similar in type and order of severity to that caused by the parent substance. If the same solution is allowed to stand at room temperature for ten minutes before application to the eye it causes a negligible reaction which subsides rapidly without producing any structural changes. After the same aqueous solution has been allowed to stand at room temperature for five hours it contains the chlorhydrin, the dimer, and the hydrochloride derived from the original substance and by this time the solution has regained considerable activity. Studied separately, the dimer is

found to be relatively inactive, while the other two products resemble the parent substance in activity.

B. The Clinical Effects produced in the Eye by the action of Chemical Substances.

Although the effects of many different agents were observed from time to time, only a few substances could be studied in detail. The agents encountered may be classified as follows:-

a. Lacrimators. (e.g. bromobenzyl cyanide and chloracetophenone.)

b. Nasal Irritants. (e.g. diphenyl chloroarsine and diphenyl cyanorarsine)

c. Vesicants. (e.g. β chlorvinyl dichlorarsine and ββ dichlor diethyl sulphide.)

d. Miotics. (e.g. diethyl fluorophosphonate.)

e. Screening Smokes. (e.g. chlorsulphonic acid.)

f. Burns due to Inorganic Substances. (e.g. hydrochloric acid and caustic soda)

G. Burns due to Flame. (e.g. explosion of chemical substances)

(1) General Considerations.

Sensory Irritation. The effects produced by noxious chemicals on the eye depend to some extent on the presence or absence of sensory irritant properties in the substances.

A vapour having such properties and in sufficient concentration causes immediate involuntary closure of the eyelids which remain in spasm and so protect the eye from further irritation. Lacrimatory vapours induce a profuse flow of tears which tend to wash the irritant away from the corneal surface and they have little

opportunity to injure the eye owing to the rapidity with which the protective mechanisms are called into play. Other active vapours of vesicant substances, however, are more insidious in effect on account of the absence of sensory irritant properties. The patient is unaware of their proximity to the eye during exposure, and it is only after a latent period of some hours when inflammation is established in the tissues that symptoms are noticed. At this stage irritation or even pain, lacrimation, blepharospasm and photophobia may be present, but the flow of tears and closure of the lids have no protective value since damage to the tissues has already occurred.

If noxious chemical substances reach the eye in solid or liquid form, sensory irritant properties afford little protection. The usual result of gross contamination is a severe inflammatory reaction which leads in the absence of a specific antidote to loss of the eye.

Pain. No pain is felt when the eye first comes into contact with chemical substances in the vapour phase. On sudden exposure to a very high concentration of lacrimatory gas such as a droplet cloud of bromobenzyl cyanide, a cold sensation is experienced momentarily at the surface of the eyes, the lids close and tears begin to stream.

The position is not so clear, however, as to whether splash contamination with chemical substances in the liquid phase will produce immediate pain in the eye. It is thought that liquid mustard gas may enter the eye without causing pain at the moment of contact, while some

consider that contamination of the eye with liquid Lewisite will cause immediate severe pain. It was impossible to decide this question from the evidence of animal experiments, but an impression was gained from several species of animals that the entry of liquid Lewisite into the human eye might not be appreciated at onee by the patient as a grave catastrophy, although it is probable that some pain would be experienced. It was exceptional for an animal to squeal when liquid chemicals were placed in the eye; squealing was noted occasionally when bland therapeutic agents, such as albucid, were instilled.

Blepharospasm. The introduction of vesicant chemical substances into the eye would be expected to cause severe blepharospasm. Even after ocular contamination with liquid Lewisite, However, several species of animals were observed to open the affected eyes voluntarily within about thirty seconds. Severe blepharospasm was never encountered in animals and the eyelids could be opened until the inflammatory reaction was well established in the eye.

The Site of the Injury. After exposure to vesicant vapours the signs of injury are first seen in the interpalpebral parts of the cornea and conjunctiva. Lesions due to liquid contamination vary more in their location. In the case of a small droplet the lesion may be severe but strictly limited, whereas, in the event of more gross contamination the agent may be spread by lid movements to involve the whole surface of the eye in its anterior segment. The human eye tends to roll upwards involuntarily at the approach of danger and this may determine the site of the lesion at

the lower portion of the limbus in some cases of splash injury.

The Latent Interval. After ocular injury by chemical substances there is an interval before symptoms and signs become manifest. The duration of this interval varies with different substances. The latent period is very brief after injury by arsenical substances, and is shorter following injury by nitrogen mustard ($\beta\beta$dichlor diethyl methylamine) than after mustard gas. The duration of the latent period is also shorter in cases of liquid contamination than in vapour injuries.

The Inflammatory Response. As the latent period passes, signs of inflammation appear in the eye. In the early stages the ocular response presents certain clinical features which are common to different agents, and to different species of animals. In the primary phase of the reaction the affected conjunctiva becomes hyperaemic and appears red; this is followed by chemosis which may develop to such an extent that the swollen protruding membrane is pallid and few vessels are seen. Serous discharge exudes from the conjunctiva and in severe injuries the lids are oedematous. The conjunctival epithelium may desquamate and then stains a yellow colour when fluorescein is applied. The cornea becomes oedematous; epithelial and endothelial bedewing may occur, while the stroma is increased in total thickness. The thickness of the cornea may be found to vary in different parts and may appear thinner in slit-lamp section in those regions where tissue damage has been greatest. Bullae may form in the epithelium, Desquamation of corneal epithelium is seen as greyish points or plaques

which take up a green colour when fluorescein is instilled. After a few days cellular infiltration of the cornea may be noted. It appears as a grey opacity advancing from the limbus or may be first seen in relation to an area in the cornea which has become ulcerated. Total necrosis and sloughing of the cornea en masse has been observed at an early stage in the goat following a severe chemical injury.

This primary acute reaction usually reaches a peak in severity during the first week, and then, if the lesion is recoverable, the inflammation begins to subside. As the conjunctival chemosis decreases the eye appears much more red from increased visibility of congested vessels, and sometimes haemorrhages may be revealed. Where the cornea has been denuded of epithelium, sliding of the remaining epithelium occurs to cover the denuded area. In this process the pigment which is normally present in the epithelium at the limbus in most animals is carried on to the corneal surface. The sliding process occupies up to about 36 hours. After a mild injury the eye appears normal in about 7 - 10 days and remains so.

In certain instances, usually when the injury has been more severe, a <u>secondary phase</u> of exacerbation occurs; a corneal lesion which has been resolving satisfactorily becomes suddenly more active in appearance. There is an increase or recurrence of corneal oedema followed by the invasion of the cornea by newly formed vessels. This has been observed to occur in rabbits at any time between the fifth and twenty-first days. Later the vessels are seen to retrogress in whole or in part and

the corneal condition becomes quiescent with scar formation. In other cases the settling process may be a troubled one with recurrent corneal ulceration over a period of seven or eight weeks. This recurrent ulceration is not to be confused with the late degenerative and ulcerative process which has been observed in the rabbit's cornea some seven or eight months after injury by mustard gas.

(2) Particular Features of certain Chemical Burns.

Although the ocular reactions produced by different burning agents have many appearances in common, they also show differences in clinical features with different types of agent.

a. Lacrimators.

(a) As Vapour or Particulate Cloud.

Lacrimatory gases act on the sensory nerve endings in the cornea and conjunctiva causing streaming of tears and involuntary closure of the lids. They bring about this result almost immediately: they act in relatively low concentration and cause no structural damage in the eye. Even in very high concentrations of vapour, however, blepharospasm is intermittent and the eyes can be opened between spasms. After an initial period of discomfort a state of tolerance may be acquired by continued exposure to a lacrimatory atmosphere.

(b) As Liquid or Solid.

It was found by animal experiments that the introduction of liquid bromobenzyl cyanide or crystalline chloracetophenone into the conjunctival sac caused a severe reaction in the eye resulting in

vascularization of the cornea. Thus lacrimator substances in sufficient dosage can produce a reaction in the eye similar to that caused by substances with vesicant properties.

b. Nasal Irritants.

Of the two sternutator substances examined, diphenyl chloroarsine was more severe in its action in the eye than diphenyl cyanoarsine applied in similar quantities, but both produced an inflammatory response of sufficient severity to lead to vascularization of the cornea in rabbits.

c. Vesicants.

The substances arranged by chemical constitution in Table 67 include many compounds with vesicant properties. By applying equal weights of these substances to the eyes of animals it was possible to classify the compounds in approximate order of activity and according to the type of ocular response as in Table 68. Four main types of response were observed:-

(a) Arsenical type.
(b) Nitrosamine type.
(c) Nitrogen mustard type.
(d) Mustard gas type.

In the case of compounds of low activity the reaction was so slight that qualitative differences may not have been revealed but only three of the substances examined produced no evidence of structural damage in the eye and their activity has been shown as 'nil' in the table. Although inactive in the sense that they do not cause injury to the ocular tissues, the fluorophosphonates were found to possess remarkable miotic activity.

(a) Response of Arsenical Type.

Arsenical substances invoke a rapid inflammatory response in the eye. A drop of liquid arsenical causes the immediate formation of a dense white opacity where it touches the cornea. The action penetrates deeply causing severe exudative iritis in the acute phase, and if the eye recovers, areas of atrophy with pigment disturbance are left in the iris presenting the picture of vitiligo iridis. While the minimal dose which will destroy the eye in the absence of treatment has not been determined, it is known that the rabbit's eye will eventually be destroyed in all cases after the entry of a drop of liquid Lewisite of the order of 0.0002 c.c.

The primary response in the vapour type of lesion reaches a peak in severity in 24 hours. At this stage of a severe lesion there is oedema of the lids, and in the conjunctiva gross oedema with haemorrhages and large areas of epithelial necrosis. Conjunctival discharge is scanty although necrotic material is plentiful. A large well-defined area of epithelial desquamation forms in the cornea with considerable oedema of the substantia propria. This is accompanied by a severe degree of iritis. Hyphaema has been reported following experimental injury with liquid arsenical substances but I have not observed this feature.

In the eyes which are mildly affected the rapidity and degree of recovery after arsenical injuries are often remarkable. In more severely affected eyes, however, the primary reaction shows little tendency to subside and maintains a high level of severity until the commencement of

the secondary phase with increase of corneal oedema. This occurs early and corneal vascularizarion has often begun by the fifth day after injury; the new vessels are numerous and occupy all layers of the corneal stroma, deep as well as superficial. There appears to be little tendency to cellular infiltration of the cornea in the aarly stages after such an injury, but often from 72 hours onwards a heavily infiltrated corneal ulcer may be found associated with a considerable amount of hypopyon and profuse conjunctival discharge.

(b) Response of Nitrosamine Type.

A group of substances resembling N carbomethoxy βchloroethyl nitrosamine in chemical constitution was examined for the property of causing ocular injury and these substances were designated the "nitrosamines". It will be seen from Tables 67 and 68 that only two compounds of this group in addition to the prototype produced an ocular response of the nitrosamine type.

When these substances are applied to the eye in paraffin solution to simulate the effects of vapour, inflammation is well established after 24 hours. Certain features of the ocular lesion appear to increase in sevenity for the first four or five days. Considerable congestion and oedema are present in the conjunctiva from the second day, but epithelial desquamation and haemorrhages are not striking features of this type of response. Conjunctival discharge is relatively prominent after 24 hours. In the cornea, epithelial staining is at first superficial and diffuse, but the areas of desquamation tend to become

larger, deeper and more demarcated after several days, while cellular infiltration extends to involve the central region of the cornea. Severe exudative iritis occurs but there are no iris haemorrhages or hyphaema. Corneal vascularization has not been observed before the seventh day.

The most active substance of this group appears to cause less reaction in the eye than Lewisite but is of the same order of activity as the prototype of the nitrogen mustard group of substances.

(c) Response of Nitrogen Mustard Type.

The first substances examined in this group was ββdichlor diethyl methylamine and it was found to be a potent eye injurant with characteristic effects. Amongst many homologues and analogues studied, only one other substance, the ethyl homologue, hears resemblance to the prototype of the group with regard to the effects produced in the rabbit's eye.

This group of substances was of particular interest in that it was possible to compare the activities of a homologous series of compounds from the methyl- to the allyl- member of the series. The power of producing eye injury decreases rapidly on ascending the series and corresponds roughly to the decrease in vesicant properties.

A drop of liquid ββdichlor diethyl methylamine of about 1 mm. in diameter causes destruction of the rabbit's eye in all cases. It penetrates the tissues of the eye so rapidly that even when irrigation is carried out immediately after contamination under ideal experimental

conditions the treatment does little to modify the severity of the resulting lesion. The entry of the liquid into the eye does not appear to cause pain, nor is there any immediate opacity formation at the point of contact with the cornea as in the case of arsenical substances.

The histological appearances of the lesion produced by a 1 mm. diameter drop in the rabbit's eye five days after contamination are seen in Fig. 29. A section from the opposite eye of the same animal is shown in Fig. 30; in this case the lesion was caused by the same dosage of liquid mustard gas introduced five days previously. This dosage of nitrogen mustard (Fig. 29) causes a marked degree of corneal necrosis, with sloughing of the superficial layers and absence of cell nuclei in the deeper layers. The anterior chamber contains a dense mass of cellular exudate including many red corpuscles. This mass is bounded posteriorly by the lens capsule, the lens having been removed from the eye before sections were cut. The effects produced in the cornea by similar dosage of mustard gas (Fig.30) present a very marked contrast. Mustard gas causes little loss of corneal tissue. The corneal stroma is densely infiltrated with cells at all levels, and the exudate seen in the anterior chamber is of fibrinous character. It is known, however, that this order of dosage of mustard gas will eventually cause destruction of the eye.

The effects produced in the iris of the rabbit by a non-destructive dose (0.025 c.c. of 1% aqueous solution) of nitrogen mustard are shown in Fig. 31.,

and may be compared with the reaction to a destructive dose (1mm. diameter drop of liquid substance) in the case of mustard gas in Fig. 32. With nitrogen mustard there is gross oedema of the iris and deep congestion of the iris vessels. Haemorrhages occur into the iris stroma. With mustard gas, even in destructive dosage, there is little evidence of any reaction in the iris.

In vapour form, nitrogen mustard causes a severe primary reaction in the cornea and conjunctiva. The response develops more slowly than in the case of arsenical substances and more rapidly than with mustard gas. Considerable oedema and numerous petechial haemorrhages are found in the conjunctiva, but discharge is not an outstanding feature. Desquamation of corneal epithelium occurs and the stroma becomes very cloudy as a result of oedema and cell infiltration. If corneal vascularization ensues, the vessels tend to invade the cornea later than in lesions due to corresponding dosage of arsenical substances and earlier than in lesions due to mustard gas.

After a severe injury from vapour the corneal reaction subsides slowly over a period of 4 - 8 weeks. Masses of degenerative material form in the anterior layers of the stroma at the site of the lesion, and there is a tendency to recurrent corneal ulceration. The epithelium is abnormally thickened over the corneal lesion; it is observed to break down from time to time with extrusion of degenerative products from the cornea.

A nitrogen mustard lesion in the rabbit's cornea five weeks after an injury from vapour is illustrated in Fig. 33. Degenerative material is in process of being extruded from the anterior layers of the corneal stroma. The posterior layers are relatively unaffected. In the final state after injury by nitrogen mustard vapour there is often much less residual scarring in the cornea than would have been anticipated from the appearances in the earlier stages of the lesion.

Nitrogen mustard differs from other vesicant substances with regard to the effects produced within the eye. Miosis occurs early and is of considerable degree. Within twenty-four hours small haemorrhages appear in the iris stroma and the iris muscles show signs of damage. At the end of twenty-four hours paralytic mydriasis supervenes. The iris is very oedematous and the vessels are deeply congested (Fig. 34). When the inflammatory reaction is severe and of rapid onset, large vesicular formations appear in the retinal layers of the iris and ciliary body caused by the collection of albuminous exudate between the cell layers. These vesicles are produced relatively easily in the rabbit's eye by inflammatory processes, and are illustrated in Fig. 35 as a result of exposure to nitrogen mustard vapour.

The stage of congestion and haemorrhage may be followed by thrombosis in the iris vessels (Fig. 36), and if the exposure has been severe there is necrosis of iris tissue. The histological appearances in the iris about six weeks after a severe vapour injury are shown in Fig. 37. The iris of a normal rabbit is shown in

Fig.38, for comparison. The affected iris is of hyaline appearance, the nuclei of the stroma cells are scanty and stain poorly, and the thickness of the iris is much reduced in patches. The chromatophores are round in form and sometimes considerably swollen in appearance. On clinical examination such an iris shows patches of atrophy; it has lost its normal colour and has a grey appearance like wet blotting paper, with absence of surface markings. In Fig. 39 and Fig. 40 are shown the two eyes of the same rabbit; the photographs were taken three months after injury. The lesion in Fig. 39 was caused by nitrogen mustard vapour, while that in Fig 40 was the result of identical exposure to mustard gas vapour. The change in iris colour and loss of surface markings following injury by nitrogen mustard are clearly seen compared with the normal appearance of the iris after injury by mustard gas.

In addition to the small haemorrhages which occur into the iris tissue in nitrogen mustard injuries, it is usual to find a large haemorrhage over the surface of the iris of the rabbit from about the tenth day onwards. In some cases bleeding occurred from the iris into the anterior chamber, while in few cases haemorrhages originated from the ciliary processes and free blood spilled through the pupil into the anterior chamber to form a large hyphaema. In the process of recovery such large haemorrhages on the surface of the iris may become organised. Subsequent contraction in this organised mass may lead to partial or complete retraction of the free border of the iris, towards the angle of the anterior chamber.

Sometimes there is ectropion of the pigment layers of the iris. The clinical appearance in partial retraction of the iris is shown in Fig.41 while Fig. 42 shows the appearance of an eye in which complete retraction has occurred The photographs were taken three months after the injury. The eye shown in Fig. 42 was examined histologically; sections were taken through the retracted portion of the iris (Fig. 43). The iris stroma is of hyaline appearance with absence of structural detail. A band of fibrous tissue lies on the surface of the retracted portion, representing the final stage of organisation of a large haemorrhage.

The Ethyl- homologue of nitrogen mustard does not cause large intraocular haemorrhages of this type although its action on the eye resembles the parent substance with regard to other features.

(d) Response of Mustard Gas Type.

From observations in several species of animals it is probable that a drop of liquid mustard gas entering the eye causes irritation but no pain. There is no immediate opacity formation at the point of contact with the cornea as in the case of injury by Lewisite. A drop of liquid mustard of 1 mm. in diameter will eventually prove destructive to the eye of a rabbit in every case; the histological appearances at the fifth day after such an injury are shown in Fig. 32. Although penetration into the ocular tissues is rapid,early and thorough irrigation may be effective in saving the eye.

It is difficult to produce a series of identical experimental lesions of the eye using liquid mustard gas. It is an oily liquid and in contact with the aqueous phase at the surface of the eye its behaviour is capricious with regard to the localization of the lesion.

The inflammatory response develops relatively slowly after injury by vapour, and, in animals, a purulent type of conjunctivitis results. Thereis little tendency to epithelial desquamation, and petechial haemorrhages are not numerous in the conjunctiva. In the cornea, oedema may be severe and some cellular infiltration occurs; some desquamation of the epithelium takes place, but, in general there is little tendency to loss of tissue. The evidences of damage are usually most marked in the superficial third of the corneal stroma in eyes which escape destruction. In severe injuries the cornea may be affected at any level, and exudative iritis may occur.

Vascularization of the cornea is of relatively late onset and is usually of superficial type. In a proportion of severe injuries, as the primary corneal oedema is subsiding, secondary oedema of the cornea occurs followed by the ingrowth of new-formed vessels. The new vessels may exhibit characteristic changes such as dilatations and constrictions, tortuosity, haemorrhages and branches which become isolated as the main trunks retrogress. The condition gradually appears to subside but leaves considerable residual scarring in the cornea. In some cases cholesterin deposits and fatty changes appear in the scars. Cholesterin crystals

may lie in plaques at a deep level forming an opacity like frost on a pane of glass. When the degenerative changes occur in the superficial stroma the cornea may be subject to recurrent attacks of ulceration over a period of many months. I have not observed late degenerative changes of this type in the cornea as a sequel to injury by other chemical substances.

d. Miotics.

When the cornea is injured by chemical substances, iris hyperaemia and pupillary constriction are observed. Nitrogen mustard (ββdichlor diethyl methylamine) causes marked pupillary constriction and will rapidly overcome the effect of atropine. The pupil of a rabbit is shown fully dilated after instillation of atropine in Fig. 44. If a drop of liquid nitrogen mustard (0.0002 cc.) is then placed on the cornea the atropinised pupil becomes constricted; the degree of constriction after an interval of thirty minutes is seen in Fig. 45. The initial miosis produced by nitrogen mustard is followed by paralytic mydriasis associated with damage to the sphincter muscle of the iris.

The alkyl fluorophosphonates have a very marked miotic action on the eye even when applied in the form of relatively dilute vapour. Introduced into the conjunctival sac by the paraffin solution method to simulate high vapour concentration they have a strong miotic action but do not cause any structural damage in the ocular tissues of a rabbit. The systemic effects resulting from the application of liquid diethyl fluorophosphonate to the eyes

of various species of animals have already been mentioned.

While I did not have the opportunity to study in detail the miotic effects of the fluorophosphonates, I experienced personally an extreme degree of miosis of about ten days duration after being exposed for about three hours to a very weak concentration of the vapour of the diethyl- compound in the course of laboratory work. Partial relaxation of the constriction was found to occur after a short period in a very dark room.

e. Screening Smokes.

The effects of exposure of the eyes to various screening smokes were observed in a few cases in the human, but were not made the subject of special study in animals. These substances, in the concentrations used for screening, have little significance with regard to their action on the eye. Chlorsulphonic acid, in screening concentrations, causes a slight degree of conjunctival irritation after prolonged exposure, while pitch smoke causes congestion of the lid margins sometimes resulting in the formation of styes.

f. Burns due to Inorganic Substances.

The effects of accidental contamination of the human eye with ordinary inorganic acid and alkaline substances were occasionally observed. These injuries occurred amongst laboratory staff who were well aware of the risks of chemical injury and for whom first-aid facilities were readily available. The lesions were of mild type and showedno ocular features worthy of

comment. In all cases irrigation was carried out promptly and thoroughly at the site of the accident and this probably decided the mild course of the lesions together with the fact that contamination was never of a gross and overwhelming degree.

g. Burns due to Flame.

Explosions occurred occasionally during the handling of chemical substances in the laboratories. The flame so generated caused scorching of the face and lids, with singeing of the hair, eyebrows and eyelashes. The injury was followed by hyperaemia and oedema of the conjunctiva, together with superficial oedema and desquamation of the corneal epithelium. In the absence of wounds of the eye complicating the injury, such lesions were found to heal rapidly after the primary inflammatory response.

(3) Hypersensitivity to Chemical Substances.

Idiosyncrasy was not observed with relation to the effects of chemical substances on the eye. Allied to this, however, is the phenomenon of hypersensitivity in which the skin and conjunctiva become sensitive to very small doses of the exciting agent. Such effects were known to be caused by mustard gas but were also observed in the case of nitrogen mustard. A very mild exposure of the order of 5 $mg.min/m^3$ of nitrogen mustard was found to produce transient conjunctival hyperaemia in a hypersensitive individual after a very short latent interval of approximately twenty minutes. The presence of conjunctival hyperaemia of early onset and transient duration confined to the exposed areas and associated with an absence of any

evidence of damage to the corneal epithelium on careful examination by slit-lamp, would favour a diagnosis of a hypersensitivity reaction in an eye which had been exposed to vapour.

(4) Ointment Bases for use in the Eye.

The experimental studies included three types of base:-

(a) Fatty bases. (e.g. anhydrous lanolin)
(b) Aqueous bases of Vanishing Cream type. (e.g. Lanette wax)
(c) Mucilages. (e.g. gum tragacanth)

All three types of base are only slightly irritant in doses of approximately 50 mg. applied to the human eye, but when used in large excess (about 0.5 ml.) in the eyes of rabbits Lanette wax causes a reaction in the cornea. In the mucilage type of preparation separation of the ingredients tends to occur under extreme conditions of storage.

C. Therapeutic Measures in Chemical Injuries of the Eye.

In general the effects produced by chemical substances in the eye are much more serious when the substances reach the eye in the form of liquid than in the form of vapour. It is important to make this differentiation with regard to the physical state of the substance when considering the rational therapeutic approach.

(1) Management of Splash Injuries. When it is possible to influence the outcome by therapeutic measures, the fate of the eye appears to depend on the promptness and efficiency with which first-aid treatment is carried out at the time of the incident. Except in the case of arsenical

vesicants, no antidote is known which is at the same time permissible to put into the eye. Immediate and thorough irrigation of the eye is still the only method of averting serious eye injury from a splash of other chemical substances. Even this measure is unlikely to modify the course of the lesion if a delay of five minutes occurs before treatment is begun. Later treatment should be on the same general lines as for vapour cases.

(2) Management of Vapour Injuries. Eyes injured by chemical vapour are not usually seen until after the latent period by which time there is an established lesion. Irrigation is useless at this stage and may even by harmful. The problem is no longer that of neutralizing a chemical substance in the tissues, but rather how to promote recovery in the damaged tissue with the least possible visual defect.

A scheme was approved by the Panel of Ophthalmic Specialists under the Ministry of Supply during the recent war as a guide to the management of cases of mustard gas injury of the eyes; it has a general application in cases of chemical injury and has been reproduced in tabular form in Table 69.

(3) Irrigation.

The nature of the irrigating fluid, provided it is bland, is of much less importance than the promptness with which treatment is begun and the thoroughness with which it is carried out. The virtue of treatment by irrigation appears to lie in the mechanical removal of irritant liquids from the surface of the eye and

from the conjunctival sac by means of a steady stream of fluid applied at the earliest possible moment and continued for about twenty minutes. Plain water, applied effectively, gives just as good results as more elaborate acid and alkaline lotions. It has the further advantage of being usually available in adequate quantity at the site of the accident. While irrigating the eyes the lids should be everted and, when one eye only has been contaminated, care should be taken to direct the flow of water away from the sound eye.

Irrigation saves the eye of a rabbit after application of a destructive dose of liquid mustard gas if treatment is begun within two minutes of contamination. In the case of arsenical substances and nitrogen mustard, however, even immediate irrigation does not prevent loss of the eye after a destructive dose. In the absence of an effective antidote it is the only method available and should be carried out at once as a first-aid measure in all cases of splash injury of the eyes by chemical substances. Experimental evidence, however, shows that once the inflammatory reaction is established, irrigation is useless and even harmful, and it has therefore no application in vapour injuries of the eye.

(4) Antidotes.

One of the most important results of research in the field of chemical injuries was the discovery of an antidote which is effective, if used in time, against arsenical vesicant substances (Peters,

Stocken and Thompson, 1945). This substance is dimercapto-propanol (syn. B.A.L., Mercaprol). The antidote does not injure the normal human cornea but may cause irritation of a few hours duration when applied to the normal eye in therapeutic dosage. It is effective against all the arsenical substances shown in Table 67, but is of no value against contamination of the eye by non-arsenical vesicants such as liquid mustard or nitrogen mustard. The antidote may be used in solution (10% in ethylene glycol) or as an ointment. These preparations must be introduced into the conjunctival sac at the earliest possible moment after contamination since prompt use alone can save the sight. But while speed is all important in order to minimise the severity and duration of the condition, treatment is found to be well worth while up to thirty minutes after contamination. In view of the irritancy of the preparations repeated applications might be inadvisable although it has been shown that the antidote can be instilled three times at intervals of thirty minutes with beneficial results. The use of repeated applications of antidote, however, does not compensate for any delay in making the first application.

It was found that the permissible interval of time between contamination of the monkey's eye and application of the antidote, in order to ensure complete recovery, was between fifteen and thirty minutes. These results were obtained with animals treated while still under general anaesthesia, and do not take into consideration the fact that spasm of the orbicularis muscle might reduce

the amount of antidote gaining access to the eye in the absence of an anaesthetic.

The efficiency of the antidote is well illustrated in Figs. 46 and 47. Each eye of a monkey was contaminated with 0.0002 c.c. of liquid Lewisite applied in the centre of the cornea. After fifteen minutes had elapsed 0.5 cc. of the antidote was introduced into the right eye and a similar measured quantity of the vehicle alone was introduced into the left eye. Fig. 46 shows the condition of the eyes five hours later; the difference in reaction is striking. The same animal is seen in Fig. 47 after an interval of thirty days. The treated eye is of normal appearance, while the control eye has a very severe corneal lesion.

No effective antidote is known for nitrogen mustard substances. Various substances such as amyl nitrite, sodium sulphite and phosphomolybdic acid were examined on theoretical grounds but were without beneficial effect on the ocular lesions.

Similarly there is no known antidote for mustard gas. Free chlorine is known to react with mustard gas, but irrigation of mustard-contaminated animal eyes with 1:500 aqueous solution of chloramine T had been found to be ineffective. It was considered that a few drops of a much stronger solution would be more likely to provide the available chlorine necessary for interaction with mustard gnd at the same time might be permissible in the eye. The most effective solution tested was chloramine T 10% in

ethylene glycol. When a few drops of this solution were introduced into the eyes of rabbits two minutes after the application of a destructive dose of liquid mastard gas, a certain number of eyes were saved from destruction. This result is of theoretical interest only since a similar effect may be obtained by efficient irrigation using plain water after a delay of two minutes.

(5) Mydriatics.

Mydriatic substances were occasionally employed in accordance with the general principles governing their use. In the mild type of vapour injury which occurred from time to time amongst the scientific staff they appeared to help in relieving ocular discomfort and congestion.

(6) Control of Infection.

Chemical injuries of the eye may be further complicated by the occurrence of secondary infection. It was found that such infection could usually be controlled by chemo-therapeutic substances such as albucid soluble and penicillin. As compared with chemo-therapeutic substances, other antiseptics in common use were found to be astringent and caustic in their action on eyes injured by vesicant chemical substances and are contra-indicated for this reason.

PART 2.

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PART 3.

"And although the arguing from Experiments and Observations by Induction be no Demonstration of general Conclusions; yet it is the best way of arguing which the Nature of Things admits of....."

Sir Isaac Newton, Opticks, 1730

PART 3.

BURNS OF THE EYE. A SURVEY OF THE LITERATURE.

1. Introduction.

Burns of the eye have been the subject of many contributions to ophthalmic literature. Most of the early papers deal with the effects of inorganic chemical substances on the eye, but within recent years more interest has been taken in the organic compounds which are being used on an increasing scale in modern industry.

It is proposed to review the literature with particular reference to those agents discussed in Part 2 of this thesis, but mention will also be made of other papers having reference to Part 1.

2. Statistical Considerations.

Garrow (1923) made a statistical enquiry into 1000 cases of eye injuries admitted as In-patientsto Glasgow Royal Infirmary. Burns of the eye accounted for 8 cases out of 145 injuries in children and in this group there were no cases necessitating enucleation of the eye as a result of ocular burns. In adults 4 cases of ocular burns occurred amongst 148 cases of non-occupational injury to the eye, and 2 of those cases resulted in enucleation. In the whole series of 1000 cases Garrow recorded 110 cases of ocular burns (11%) and pointed out that there is a low enucleation percentage rate (9.09%) for this class of injury.

Würdemann (1932), analysing the causes of ocular

injury in a series of 359 cases, found 60 cases of burns (17%).

In a series of 3650 cases suffering from industrial eye injuries Minton(1936) recorded 50 cases of chemical burns of the conjunctiva and cornea, giving a proportional rate of 0.88% Commenting that such injuries were rare, he attributed this to the fact that few chemical factories were situated in the vicinity from which the population was drawn. Lime burns accounted for 20 of the 50 chemical injuries. Minton also recorded 30 cases of electric welding conjunctivitis in this series of industrial eye injuries.

The rate of occurrence of eye injuries in chemical industries is given by Dickson (1943) as 13% per annum. No detailed analysis was made of the cause of the injuries.

From data collected in the Illinois district in 1939, Kuhn (1944) shows 104 cases of ocular burns amongst 824 eye injuries (about 12.5%).

These figures show that burns of the eye account for about 11 - 17% of all injuries of the eye, while the proportional rate of occurrence of chemical burns calculated by Minton for a hospital out-patient population is of the same order as that found in the case of ocular burns in Part 1 in a similar population.

3. <u>The Investigation of Toxic Hazards</u>.

The methods available for the investigation of the effects of chemical substances on the eyes have been discussed at some length in Part 2 of this thesis. I have

not been able to find any papers in the literature dealing with this aspect of the subject.

Goldblatt (1944) discusses the general approach to the investigation of toxic hazards in industry, but his paper contains no reference to ocular hazards. He reviews the subject in a broad manner and defines four methods of discovering the physiological properties of toxic or suspected material.

1. Search of the Literature.
2. Study of the Physical and Chemical Properties of the Materials.
3. Experimental study.
4. Clinical Investigation.

The methods are discussed in good perspective and the paper is of value as a background to experimental and clinical studies of this kind.

4. Clinical Considerations.

(1) Lacrimators.

Cullumbine (1946) describes the effects produced in human subjects exposed to lacrimatory vapours. A visual test based on the rangefinder was used for the quantitative assessment of the harassment caused by these substances. It was found that for each lacrimator tested there was a critical concentration above which any further increase in concentration did not produce a significant increase in harassment. Moreover it appeared that in each case the critical concentration caused a similar intensity of harassment, namely, about 50%. (100% harassment was taken as complete inability to see for the duration of the test).

When exposed to lacrimatory vapour the subject is unable to see mainly on account of blepharospasm, but blepharospasm was found to be intermittent even during continued exposure. An intensity of harassment of 50% was taken as equivalent to a subject being unable to see during half the time of the test.

It was also noted that the human eye could become "tolerant" with regard to both lacrimation and blepharospasm in a given lacrimatory atmosphere, no matter what the chemical nature of the atmosphere, and whether the concentrations were high or low. The time taken for different subjects to acquire tolerance varied enormously e.g. from 2 - 40 minutes, and this time seemed to bear no relation to the concentration of vapour or to the nature of the lacrimator substance. Tolerance was acquired whether the concentration was slowly rising or slowly falling, but a sudden marked increase in the concentration of the lacrimatory atmosphere broke down the tolerance. About a quarter of the subjects showed a tendency to relapse from the tolerant state, and in about a third of these the relapse was of a phasic nature - i.e. lacrimation tended to return and pass away periodically during the exposure.

(2) Vesicants.

a. Arsenical Substances.

In a study of Lewisite lesions of the eyes of rabbits, Mann, Pirie and Pullinger (1946) compare the characteristics of the ocular lesions in Lewisite and Mustard gas injuries. Differences in the rapidity of the ocular response, the pupillary reaction, and the order of magnitude of the destructive dose are described for the two substances.

Stress is laid on the chronic nature of the corneal lesions in mustard gas injuries, associated with the presence of characteristic deformed vessels in the cornea and conjunctiva, and in a proportion of cases with the formation of cholesterin and other lipoid scars. This is contrasted with the Lewisite injury where the lesion runs a definite course to recovery or destruction, where saars are fibrous and where there may be proliferation of conjunctival pigment. In mustard injuries the iris is relatively little involved and there are no late pigment disturbances. Lewisite causes severe iris involvemant followed by some depigmentation and atrophy of the iris stroma. The authors also contend that lesions strictly confined to the cornea and not involving the limbus do not vascularize in the case of mustard gas, whereas with Lewisite, vascularization of the cornea is independent of the site of the primary lesion and occurs when a sufficient dose of Lewisite reaches either the cornea or the limbus. It is thus implied that the localization of site of a mustard gas injury determines corneal vascularization, but in a Lewisite injury corneal vascularization is dependent on the quantitative dose.

Certain features of the papers are worthy of further comment and consideration. It was found that the dosage of Lewisite vapour given by local applicators was impossible to standardize. This is in agreement with my own experience in the use of applicators but does not affect the result described in the paper since most of the

observations were of a qualitative nature.

Again it is stated that although the application of mustard gas to the eye is not painful, pain is experienced with Lewisite, but there is little evidence in the paper on which to assess this point.

With regard to the stimulus invoking corneal vascularization several views may be taken. The authors demonstrate that the entry of new vessels into the cornea, after mustard gas, depends on the localization of the site of the primary injury. In contrast, they state that corneal vascularization after Lewisite is independent of the site of the injury, but depends on a sufficient dosage being applied to either the cornea or the limbus. These observations are both consistent with the hypothesis that the substances differ in their ability to penetrate the ocular tissues. There is no doubt that Lewisite has a rapid and severe action within the eye, resulting in permanent structural changes in the iris, whereas mustard gas causes relatively little reaction in the iris even when applied in relatively high dosage, although it has a very marked action on a vascularized tissue such as the conjunctiva, in which new-formed vessels may appear. Associated with this apparent difference in penetrability, new vessels appear at all levels in the cornea after Lewisite injury, but in mustard gas injury they take origin from the limbus vessels only and tend to lie superficially in the anterior layers of the corneal stroma. This supports the view that Lewisite penetrates the ocular tissues with ease and may act directly

on the iris, while mustard gas appears to penetrate the cornea only with great difficulty and is probably absorbed in great part in the superficial stroma.

It would be unsafe to assume that changes in the endothelial pattern of the cornea appearing soon after a chemical injury must indicate that the substance has passed through the cornea to reach the aqueous. Further, the presence of localized congestion in the iris vessels and a slight degree of miosis, noted by the authors after mustard gas injury, could be accounted for by antidromic nervous impulses resulting from an injury confined to corneal tissue.

Uhde (1946) reports 8 cases of ocular injury by Lewisite vapour amongst workers at Edgewood Arsenal. These burns were very mild. A case of contamination of the eye with a mixture of chemicals containing Lewisite is also described. The affected eye was very painful but the degree of blepharospasm can not have been sufficient to interfere with efficient irrigation, since the author states that this was thoroughly carried out for about twelve minutes immediately after the accident. It cannot be assumed that the pain experienced was due to the Lewisite fraction of the contaminating mixture which entered the eye. Arsenical antidote was not available and the injury resulted in leukoma adherens with extensive nebular scarring and serious reduction in vision.

Other cases of ocular injury from Lewisite are reported by Scherling and Blondis (1944); 5 cases sustained vapour injury while 2 cases were injured by liquid Lewisite.

The authors found that Lewisite produces immediate ocular irritation. Since the antidote was instilled with little loss of time in these cases none of the eyes was seriously affected.

b. Mustard Substances.

A description of the clinical features of the ocular lesions produced by Nitrogen Mustard substances has not been found amongst the available literature, although the pathological changes resulting from liquid contamination of the eyes of rabbits have been reported in the case of certain Nitrogen Mustard compounds.(LaMotte and Leopold, 1946)

On the other hand there is now a considerable volume of literature on the subject of Mustard Gas injuries of the eye. It is proposed to discuss only a few of the more recent contributions and to concentrate attention on some of the problems which are still unsolved.

The published literature has been reviewed conprehensively by Hughes (1942). It was shown by the official records of the First World War of 1914-18 that 75 - 90% of all mustard gas casualties presented some degree of ocular involvement. These cases could be divided into three groups:-

1. Mild conjunctival irritation, subsiding in 1 - 2 weeks with symptomatic treatment..... 75%

2. Conjunctival chemosis and roughening of the corneal surface in the exposed area but no staining with fluorescein. Recovery in 4 - 5 weeks..... 15%

3. Corneal erosion. Convalescence 2 - 3 months..... 10%

While there was a low incidence of serious immediate complications, it was well established that in some cases corneal ulceration recurred as long as seventeen years after the original injury when this had been of severe degree.

Dealing with certain experimental aspects of mustard burns Hughes discusses the dose necessary to produce lesions. In the case of liquid mustard he does not mention its capricious behaviour in the eye and the difficulty which is encountered in attempting to obtain standard and reproducible lesions although he stresses the variations which are observed in the sensitivity of different species of animals. With regard to vapour effects attention is drawn to the fact that the severity of ocular lesions is dependent on the concentration of vapour and the length of exposure. It is noted that the eyes react to much lower concentrations of mustard vapour than the skin.

Summarizing the clinical course of severe corneal burns from reported observations in the rabbit and in man, the author described five stages. He does not point out, however, that marked differences exist between the rabbit and man with regard to the duration of the course of the lesions and with regard to the time of onset of the different stages. For instance late corneal degeneration appears after a period of months in the rabbit but takes years to develop in man. Again, with regard to corneal vascularization, the time of onset in man has not yet been firmly established.

Mann and Pullinger (1942) made a detailed study of the effects of mustard gas on the eyes of rabbits; in the

same paper Mann describes the clinical pathology of mustard gas injuries to the human eye and correlates the findings with the effects observed in rabbits. In the animal experiments liquid mustard was applied in similar dosage to the cornea, and the corneo-scleral junction.

The uncomplicated corneal lesion. Attention is drawn to the erratic behaviour of liquid mustard when it is placed on the cornea. The authors developed a technique of touching down a small quantity of liquid mustard from the end of a glass rod at a series of spots (3 to 9) on the corneal surface, the lids being held apart for 15 minutes when no mustard can be seen remaining on the corneal surface. It is claimed that the lesions so produced are likely to be comparable with those expected in man. While this technique produces lesions admirably suitable for detailed slit-lamp studies it may be criticised that such lesions are very unlikely to occur in the human where reflex blinking occurs immediately following the entry of foreign material into the eye. It would be unsafe to stress analogy between such lesions and those caused by accidental splash contamination in a factory.

From slit-lamp studies of the central corneal lesion the authors claim that liquid mustard penetrates the cornea with remarkable rapidity. This appears to be based on the development of visible reaction in the deeper corneal layers and in the iris. Since injury to the superficial layers of the cornea from a non-penetrating foreign body can cause a reaction in the deeper corneal layers together with

hyperaemia of the iris, it would seem unsafe to assume from appearances of this kind that a noxious agent had penetrated the corneal tissue to reach the iris. It was observed that the substantia propria, though permanently altered, is not cast off as a slough, and after a brief period of oedema, returns to its normal thickness though it still shows a pathological change which may be permanent. Oedema is a prominent feature of the corneal lesion and there is an absence of new vessel formation.

The lesion involving the corneo-scleral junction. Droplets of liquid mustard were touched down on the cornea in the shape of a V with the ends of the two limbs on or near the limbus.

Although the section of the iris underlying the corneal lesion became hyperaemic in about six minutes, the whole iris was not involved for five hours and an aqueous flare was not noted until seven hours had elapsed. These facts appear to argue against direct permeation of mustard liquid through the cornea and aqueous to the iris.

New features observed in lesions at this site were conjunctival discharge, healing of areas denuded of epithelium by sliding of epithelium from healthy parts, carrying pigment from the limbus over the corneal surface, and the onset of a phase of secondary corneal oedema associated with the invasion of new vessels into the stroma.

Describing the new vessels the authors note that "although the vessels in the cornea are at varying depths they all originate from the superficial conjunctival vessels

and not from scleral branches". They also observe that "the new vessels grow in as fine straight vessels with tapering ends" but that once in the cornea the blood appears to clot in many of the tapering ends, while "some of the invading vessels have bulbous ends and assume fantastic shapes, detached points, branches and islands of blood being constantly formed, disappearing and reappearing rapidly - the whole pattern varying from day to day, always extending further into the cornea, and always accompanied by secondary oedema".

If it is true that liquid mustard rapidly penetrates the cornea to have a direct action on the iris, then the absence of the deep vascularization usually associated with uveal lesions is noteworthy. The abnormal vascular forms can be interpreted in either of two ways. Mustard gas may affect the vasculature at the limbus from which the new vessels arise, resulting in the appearance of a mutation later in the rapidly growing derivative vessel buds. Alternatively the chemical may affect the corneal tissue so that healthy new vessels entering the area later react to the altered environment by the development of abnormal forms.

In lesions of greater severity, recurrent thromboses and persistent blood islands were observed, and retrogression of the vascularization was associated with the deposition of fat and cholesterin crystals. When the latter were laid down in the superficial stroma they led to recurrent attacks of corneal ulceration. The authors comment that

amongst these changes the most characteristic are the blood islands and the peculiar varicosities seen after subsidence of the acute stage, together with the ulceration of the superficial cholesterin deposits in the absence of fat.

Discussing the effects of mustard gas injuries to the human eye Mann divides the cases into five groups depending on the severity of the lesion; the series includes injuries by vapour and liquid.

1. Extremely mild cases. Conjunctiva alone affected.
2. Mild cases. Conjunctiva hyperaemic and corneal epithelium injured.
3. Severe cases. Corneal epithelium and substantia propria oedematous. Involvement of the conjunctival vessels, especially the limbal supply.
4. Very severe cases showing late corneal ulceration.
5. Extremely severe cases showing corneal perforation.

The authors conclude that the effects of vapour and liquid are different only when the amount of mustard gas which soaks into the tissues is different, i.e. the difference is quantitative only. They also observe that late keratitis in man is seen as a degenerative ulceration depending on the initial damage sustained by the limbus and cornea and not on any continued action of mustard gas or any of its breakdown products. The histories given by Mann's very severe cases bear a close resemblance to that of A.McW (Table 1, serial No. 92), a case of late corneal degeneration from mustard gas. In this case, however, there was no evidence of any corneal vascularization or damage to the

limbus, such as is claimed by Mann and Pullinger to be necessary for the development of late corneal degeneration.

Scherling and Blondis (1944) describe the effects of mustard gas vapour and liquid on the human eye. In a case in which a splash of liquid mustard entered the eye causing a corneal lesion about 3 mm. distant from the limbus, the eye was still subject to recurrent corneal ulceration after a period of three months, but "the conjunctiva was normal in appearance except for several minute aneurysmal dilatations that persisted and there was no vascularization of the cornea". These authors comment that "the absence of exudate and cells in the aqueous and of changes in the iris is provocative evidence that the products of corneal breakdown are not toxic if absorbed into the aqueous and that mustard gas does not pass unchanged through the cornea".

d. Miotic Substances.

The effect of di-isopropyl fluorophosphonate (D.F.P.) on the normal eye has been investigated extensively during recent years, but so far few papers have been published. Leopold and Comroe (1946) confirm the intense, prolonged miotic effect resulting from instillation of D.F.P. into the conjunctival sac in several animal species (rabbits, cats, dogs, and man) and note quantitative differences in the response. They found that the effect was most marked in man. Maximal pupillary constriction occurred after 0.1% solutions of D.F.P., while no effect was obtained on the pupil with concentrations below 0.01%. The speed and intensity of the pupillary response to 0.1%

D.F.P. was observed to be of the same order as that produced by 1% eserine but the duration of the response was found to be much greater than that of any other known miotic agent. D.F.P. produced ciliary spasm and "false myopia" for about 48 hours, and a single application of 0.1% caused a fall in intraocular tension which lasted about 8 days.

Ciliary ganglionectomy was carried out in a series of cats, and after allowing time for degeneration of the postganglionic fibres it was found that 1% D.F.P. had no effect on the pupil of the denervated side. There was no evidence of any direct action on the ciliary muscle itself.

The effect of solutions of D.F.P. on human eyes fully under the action of mydriatics such as homatropine and atropine was observed, and it was noted that only 0.2% solution of D.F.P. was required to overcome the action of 1% atropine on the muscles of the iris and ciliary body.

Investigating for toxic effects from systemic absorption following instillation of D.F.P. in man it was found that some absorption did occur as evidenced by a fall in plasma cholinesterase content. Despite a very low plasma cholinesterase, symptoms do not appear in man after a single dose of D.F.P. They may appear, however, if the red cell cholinesterase is reduced to about 75%. The authors point out that this does not mean that significant absorption will not follow the frequent, indiscriminate use of D.F.P.

The substance was found to be equally effective in solution in water and in peanut oil, but was more stable in the latter vehicle.

It appears, therefore, that relatively weak solutions of D.F.P. have an eserine-like action on the intraocular musculature, and will overcome the effects of mydriatics such as homatropine and atropine. A prolonged fall of intraocular tension results in the normal eye. The passage of a nervous impulse appears to be necessary for the action of D.F.P. since it has no effect after denervation of the musculature; this supports the observation (Part 2) that if the stimulation of light is withdrawn whilst the eye is still under the influence of D.F.P. some dilatation of the pupil will result. The substance can have a marked systemic effect in certain animals as a result of conjunctival instillation and from the above observations in man it would seem that the indiscriminate use of this substance as a miotic might have serious consequences.

d. Mydriatic Substances.

On account of the possibility of a serious shortage of the usual mydriatics, as a result of the war, a series of relatively simple compounds was prepared, which might be expected to show mydriatic properties. From animal experiments it was concluded that dimethylaminoethyl benzilate ethochloride was an efficient atropine substitute and Riddell (1946) gives an account of its clinical trial in 1% solution. This substance was referred to as E.3., and was found to be an efficient substitute for homatropine, both as a mydriatic and a cycloplegic. In addition no skin irritation resulted from its use in subjects known to suffer from atropine sensitivity, and no changes were found in the

corneal epithelium.

e. Inorganic Substances.

Friedenwald, Hughes and Hermann (1944) found by experiment that the corneal epithelium in the rabbit had a highly protective effect against the penetration and damaging action of acids, and that the corneal stroma had some buffering capacity for solutions below pH 4.0. Ocular lesions were produced however, by exposure to isotonic solutions of hydrochloric acid of pH 2.5, or by exposure to isotonic solutions of citrate-phosphate buffer at pH 4.5 or below,

In further experiments with acids the same authors observed the following special characteristics of acid burns in contrast to burns with alkalis and indelible dyes:-

1. Somewhat slower penetration into the eye with rather sharp demarcation of the lesion.

2. A clinical course which can be prognosticated with some acuracy within a few hours after the injury. (i.e. a lesion of non-progressive type.

3. Little tendency for the corneal epithelium to desquamate.

4. Little tendency to exudative manifestations such as purulent discharge, with or without secondary infection, intense leucocytic infiltrations of the conjunctiva, cornea and iris, or fibrinous iritis.

5. Little evidence of selective involvement of the blood vessels, e.g. production of intense early oedema or petechial haemorrhages in the conjunctiva or, later, ischaemia and thrombosis of vessels around the limbus and in the iris.

6. Marked tendency for the relatively opaque cornea to heal.

7. No early loss of corneal mucoid as shown by metachromatic staining with toluidine blue and determination of the hexosamine content of the cornea; after one week, however, metachromatic staining disappeared in the scarred areas and hexosamine content was reduced.

They concluded that, acid burns of the cornea are essentially non-progressive and late relapses are uncommon.

With regard to alkali burns, on the other hand, it is well known that the ultimate prognosis cannot always be estimated at an early examination since in many cases of apparently mild burns late infiltration, necrosis, or ulceration of the cornea develops. Reviewing the literature and summarising the present knowledge on the subject of alkali burns of the eye, Hughes (1946) describes the main characteristics of such a burn and discusses the factors governing the severity of the lesion. Alkali burns are stated to be progressive in type and their characteristics were observed to be rapid penetration of alkali through the cornea and early involvement of the iris and ciliary processes Marked corneal oedema developed early with loss of metachromatic staining of corneal mucoid and disappearance of stroma cells. Cellular infiltrations were also a feature of these lesions, occurring into the conjunctiva, cornea and anterior chamber. Superficial corneal ulceration tended to persist without increase of opacification and the reaction in the iris was persistent. There followed a stage of gradual recovery, or alternatively, progression of corneal opacification and ulceration associated with vascularization.

f. Thermal and Radiational Agents.

Ballantyne (1939) discussing thermal burns of the eye finds that they can be divided broadly into two groups:-

1. Flame burns or scorching; due to exploding coal gas, benzène, etc.
2. Contact burns; due to contact with incandescent objects or wood, metal or other material.

The former type of burns is often confined to the eyelids but in some cases the eyeball itself is scorched and there may be opacification of corneal epithelium. The destroyed epithelium is shed and regeneration occurs in a few days.

The contact burn, on the other hand, is apt to be more limited in extent, and deeper than the flame burn, with resulting destruction of tissue which later on may lead to scarring.

Duke-Elder (1929) studying the action of shortwaved light upon the eye, calls attention to the latent period between exposure and the onset of symptoms in photophthalmia. There appears to be no reaction during the latent period, while the commencement of corneal trouble is accompanied by all the signs of photophobia. He suggests that this is due to exposure of the free nerve endings in the cornea; if the cornea is protected during radiation, the violent conjunctivitis is accompanied by no distress; and in the more severe exposures, where the whole central cornea has been destroyed, the evidences of subjective irritation are correspondingly less. He also notes that

between the latent period and the commencement of acute symptoms, at the time when the corneal oedema is very obvious, and when typical halos are most evident, the cornea becomes practically anaesthetic.

The literature with regard to radiational cataract has been comprehensively reviewed by Duke-Elder (1940), and it is evident that cataract can be produced by radiant energy of any form. The development of the cataract appears to be preceded by a latent period, but the early stages of development and the duration of the latent period do not appear to have been investigated fully. Radiational cataracts are of cortical type and usually affect the posterior part of the periphery of the lens.

5. Pathological Considerations.

(1) Regeneration of Corneal Epithelium.

Several factors play a part in the regeneration of the epithelium, namely:-

1. Migration of cells from the edge of the defect.
2. Mitosis at some distance from the defect.
3. Sliding of surrounding epithelium over the defect.

In a study of epithelial regeneration in the living eye, Mann (1944) described the effects produced in the pigmented ring at the limbus in rabbits following injuries of various kinds. A pigment slide was observed to occur on to the corneal surface or towards the conjunctiva when an area of epithelium was damaged at less than 5 mm.

distance from the limbal pigment ring. The slide can be produced by simple trauma or by chemical injury; it is not so easily produced by heat. The shape of the slide was found to be determined by the shape and position of the epithelial loss. This type of pigment slide associated with regenerating epithelium is differentiated from pigment proliferation in response to chemical injury and from pigment migration towards the conjunctiva which occurs in cases of Vitamin A deficiency without epithelial loss.

(2) The Pathological Effects of Arsenical Substances.

Adler, Fry and Leopold (1947) studied the pathological changes produced by various war gases in the eyes of rabbits and found that all eyes exposed to severe burns by different substances showed certain common histological features. The authors emphasized the following features of the Lewisite injury:-

1. In the early stages changes appeared in the corneal stroma which may be interpreted as a rapidly progressing necrosis of the whole stromal layer. This was seen in the loss of the nuclei of the corneal fibres, the loss of staining ability of these fibres and their loss of outline. These changes were first seen at the end of six hours and reached a maximum in twenty-four hours.

2. The infiltration of the stroma began at the periphery at the twenty-four hour stage and was of polymorphonuclear cell type. This infiltrate was replaced by a round cell infiltrate at the end of the ten day stage.

3. Vascularization did not make its appearance till the end of five days. This vascularization was in all layers of the stroma but was most prominent in the middle layers. In fourteen

days the vascularization was fairly intense.

4. In a treated eye there were no changes that could be attributed specifically to the treatment. The changes were similar to those observed in the untreated eye but were of milder degree.

By injecting indicator dyes into the cornea before contamination with Lewisite, Hughes (1947) showed that there were two components in the resulting burn. He contended that Lewisite is immediately hydrolyzed at the site of contact with the moist surface of the cornea, liberating hydrochloric acid sufficient to produce a superficial corneal opacity. All the later characteristics of a Lewisite burn of the eye can be produced by the instillation of a dilute solution of Lewisite oxide (ClCH: CH.AsO) containing trivalent arsenic, held to be responsible for the progressive features of the corneal lesion. Hughes noted irreversible histological changes in the rabbit cornea beginning ten minutes after exposure and becoming well marked in thirty minutes.

(3) The Pathological Effects of Mitrogen Mustard Gas.

LaMotte and Leopold (1946) studied the effects produced by certain nitrogen mustard substances in rabbit eyes. They found that ββdichlor diethyl ethylamine in liquid form has a deep action in the eye causing severe necrosis of anterior uveal tissue, degeneration and loss of function to such an extent that any return to normal appears impossible. Trichlor triethylamine, on the other hand, has a negligible action on the iris and ciliary body, with subsequent complete return of the part to a normal

histological appearance. Their investigation did not include ββdichlor diethyl methylamine, the prototype and most active aubstance in the nitrogen mustard group.

(4) The Pathological Effects of Mustard Gas.

a. Avascular healing in the Cornea.

In experimental lesions made with mustard gas in rabbits it was found (Mann and Pullinger, 1943) that spontaneous avascular healing invariably followed when the liquid droplets damaged the centre of the cornea alone and left the corneo-scleral junction uninjured and free from oedema.

By intravenous injection of vital dyes, slit-lamp observation of the living eye, and microscopic examination of tangential sections of corneae treated en masse by impregnation of silver (Pullinger, 1943) and other stains, the authors were able to correlate the clinical with the histological findings. During the healing process a considerable amount of intra- and extra-cellular fluid was present in the epithelium, manifested clinically as "bedewing", but after a few days had passed this hydropic change was confined to the cells alone.

In the stroma a polymorphonuclear leucocytic invasion occurred within twenty-four hours. These cells migrated from the limbal vessels at all levels towards the surface of the cornea, and towards fragments of destroyed corpuscles. The cells were of linear form and their presence was independent of bacterial infection.

At the end of ten days or so when the primary corneal response had subsided a silky appearance was

observed in the slit-lamp section and this was correlated with a second cellular invasion of the stroma, this time by wandering cells, which started within forty-eight hours of the injury. Of other motile cells - fibroblasts and lymphocytes - none was ever seen unless blood vessels had at some time entered the cornea. In the early stages of healing many wandering cells functioned as macrophages but evidence was found that in the later stages these wandering cells are capable of transformation into fibrocytes, corneal fibre-forming cells, satellite cells and even into corneal corpuscles themselves.

b. Cholesterin and Fat Deposition in the Cornea.

This subject is discussed by Mann and Pullinger (1942) on a basis of observations in experimental animals and cases of delayed corneal degeneration in the human subject. They point out that the deposition of fat and cholesterin may occur not only in mustard gas injuries, but also as a sequel to severe keratitis, either infective or due to other chemicals such as sulphuric acid.

Having noted that central corneal lesions heal without vascularization it was observed that such avascular scars never contain cholesterin or fat, and it was considered that the essential factor in this degeneration is previous vascularization of the cornea. In some cases superficial vascular loops of thin even calibre crossed the limbus, extended for a time beneath the epithelium and then retrogressed, and it was found that such regular superficial vessels were never followed by deposition of fat or

cholesterin. The authors then describe the invasion by deeper vessels of bizarre shape and irregular calibre which, as the condition improved, left behind detached vessel tips and blood islands in the cornea. These somteimes disappeared by haemolysis of the blood within them, which could be observed seeping out through the endothelial wall along the lines of corneal fibrils. In a small number of cases as these vessels retrogressed a deposit of fat and cholesterin was formed beyond their disappearing tips. As the cholesterin appears it at first outlines and then obscures the empty endothelial wall of the vessel which finally disappears completely. The fat precedesthe appearance of crystals and becomes rather less in amount as they increase.

The Lipoid occurs in the following forms:-

1. As exceedingly fine droplets like an emulsion bathing the fibrils of the substantia propria, while the fibrils themselves appear to remain intact. The droplets are not doubly refracting and appear at any level in the stroma.

2. As large intracellular globules and cystals having the characters of cholesterin esters. The cells containing the crystalline lipoid are macrophages and appear in and around the deposits of emulsified fat, or when no emulsion is present.

3. As fine intracellular globules of isotropic fat, in adventitial cells and possibly endothelial cells of blood capillaries, in eyes with or without "lipoid scars".

4. As free cholesterin crystals.

The authors suggest that the emulsified lipoid and the crystalline lipoid may be quite distinct or may be stages of a process related in time since the appearances suggest

that the fine globules are ingested by macrophages and converted by them into cholesterin esters. Analogy is drawn between these processes and those occurring in the vessel wall in atheroma and it is put forward as a hypothesis that damage to the avascular or relatively non-vascular intima of vessels may be followed by the ingrowth of new capillaries which subsequently retrogress with deposition of lipoid.

(5) The Pathological Effects of Inorganic Substances.

Friedenwald, Hughes and Hermann (1946) made an experimental investigation into the effects of acid burns of the eye. Rabbit eyes were irrigated for ten minutes with a tenth-normal isotonic solution of hydrochloric acid and specimens were examined microscopically at varying intervals up to twenty-one days.

Immediately after irrigation the corneal epithelium became acidophile and the superficial cells desquamated. At forty-five minutes coagulated proteins appeared in the anterior chamber. By two hours albuminous material was seen under the corneal epithelium and the corneal stroma was mildly oedematous. After four hours the epithelium showed acidophile granules in the cytoplasm, and there was oedema in the substantia propria, but the endothelium appeared normal. After eight hours the changes had advanced and there was shrinking and disappearance of stroma cell nuclei. By twenty-four hours polymorphonuclear cells were invading the superficial layers of the stroma. Metachromatic staining revealed no appreciable loss of

corneal mucoid at this stage. On the seventh day a thin degenerative epithelium covered the burned area, superficial blood vessels were observed in the oedematous stroma, the endothelium had proliferated forming a layer several cells deep, and there was now almost complete loss of corneal mucoid. During the third week repair processes were at work and proliferating fibrous tissue, blood vessels, and inflammatory cells were found in the injured region.

In a later study Hughes (1946) described the pathological characteristics of alkali burns. After two minutes there was sloughing of epithelium, commencing disintegration of stromal cells in the substantia propria, fragmentation of corneal endothelium and iris congestion. Cellular invasion of the cornea had begun at two hours, exudates were observed in the anterior chamber and the anterior uveal tissues were oedematous. Loss of metachromatic staining of corneal mucoid occurred early at about eighteen hours after injury. Unfortunately the amount of alkali used to produce those effects is not recorded and so a detailed comparison with the pathological appearances caused by acids would be valueless. At the same time, however, the author points out that alkalis are rapid in action, have an early effect on the corneal mucoid, and the lesions tend to run a prolonged course.

(6) <u>The Pathological Effects of Thermal and Radiational Agents</u>.

In a paper on wound healing in an insect, Wigglesworth (1937) considered that the substance which

activates the sliding cells in regenerating epithelium is a tissue product of autolysis of the injured cells and also noted that it is neither tissue nor species specific. He observed that the substance is destroyed by heat. Mann (1944) found in studying epithelial regeneration in the rabbit's cornea that if, instead of removing the epithelium by scraping, the cornea is burned with a hot wire, then the amount of sliding produced is much less. She noted that the movement of limbal pigment is very irregular and does not occur all along the burned area and points out that this may support Wiggleworth's contention that heat destroys the activating substance. In an experiment making three small burns of the cornea, two were made using a hotter wire than the third. In the latter case only was a pigment slide observed to occur towards the lesion. Since all three burns healed, Mann presumed that the burns caused by the hotter wire healed by mitotic division in the cells at the edge of the burn.

Duke-Elder (1932) summarises the features of the thermal lesion caused by infra-red radiation. In the cornea it produces coagulation and opacities; in the iris, by the pigment of which much of the heat is absorbed, severe haemorrhagic congestion with paralytic pupillary dilatation results, leading to depigmentation and atrophy; in the lens an exfoliation of the zonular lamella occurs, and, in severer doses, coagulation of lens proteins and the rapid production of cataract; in the retina a necrotic burn is produced. In contrast to this is the chemical or abiotic

lesion produced by ultra-violet radiation. This is of a completely different nature, and the histological appearances of the fully-developed reaction are characteristic. In the corneal epithelium there is a nuclear chromatolysis associated with a swelling and oedema of the cytoplasm. Thereafter acidophile staining becomes evident in the nucleus, which progresses to the formation of highly refractive red granules within it; these coalesce into discrete "inclusion bodies" which may eventually replace the whole of the nucleus. At a later stage the nuclear inclusions tend to bulge the nuclear membrane outwards, and finally they may be extruded altogether from the nucleus into the cytoplasm, leaving the remnants of the nuclear membrane behind. Subsequently the cell dies and, if it is a superficial one, is desquamated. Meantime, in the surrounding tissue there is a considerable vascular reaction, associated with an eosinophilic infiltration. Two features of the process of resolution are characteristic; first the rapidity of the recovery of the traumatized cells and of the proliferation of fresh cells to replace those exfoliated, and second the comparative absence of mitotic activity in the process of repair.

Dealing with the pathology of radiational cataract v.Szily (1938) found that the duration of the latent period before the first appearance of lens opacities varies within very wide limits. Radiational cataracts were usually found to appear as cortical opacities of subcapsular type and often affecting the posterior polar region of the lens. When caused by heat and infra-red rays these changes may be

associated with separation of the outer layers of the lens capsule. Considering the cataract caused by X-ray and radium trauma, v.Szily states that this type of cataract may also begin as a posterior polar opacity or in the form of vacuoles and very fine striated opacities beneath the anterior lens capsule. Degeneration of the epithelium occurs together with granular disintregration and liquefaction of the superficial cortical layers. There is evidence to indicate that the first changes in the lens epithelium take place in the equatorial region, whereby the rays alter the reproductive capacity of the germinative cell collections, leading to the formation of atypical fibres or vesicle cells.

6. Therapeutic Considerations.

It is agreed by most observers that in chemical injuries prevention is better than cure. While prophylactic methods and counsels of perfection are apt to be disregarded, however, accidents still occur, and so the available therapeutic measures must be considered.

(1) Treatment of Arsenical Lesions.

During the war years a new compound, 2 : 3 dimercapto-propanol (B.A.L.) was discovered having an antidotal action to the arsenical vesicants. Peters, Stocken and Thompson, (1945) described the preparation of this substance. Its action in cases of arsenical burns of the eye has been intensively studied. Mann, Pirie and Pullinger (1947) investigated the effects produced by B.A.L. in the rabbit's eye using various methods of application and different strengths of solution. They found that continuous

application for fifteen minutes (as an eye bath) of a large amount of B.A.L. in strengths varying from 5% to 20% is harmful, but that a single drop of a 30% solution can be used with safety. They advocate the use of solutions between 10 and 20% in strength. Pure B.A.L. was found to have an effect similar to a 30% solution but left a very slight corneal nebula. The application of B.A.L. within five minutes to an eye contaminated with a destructive dose of Lewisite was found to be successful in preventing the action of the Lewisite. From personal observation, however, I have noted that B.A.L. may be ineffective in saving the eye if the degree of contamination of liquid Lewisite is sufficiently gross. Studying the effects of delayed application of the antidote the authors found that applications delayed for varying times up to twenty-five minutes also saved the function of the eye although partial permanent damage remained.

Scherling and Blondis (1944) describe the irritant effect of B.A.L. when applied to the normal eye, and also report on its therapeutic efficacy when applied to eyes contaminated with Lewisite in both liquid and vapour form. It is of interest to note that no mention is made of any difficulty in administering the therapeutic agent on account of severe blepharospasm, a contingency which has been anticipated by some observers on theoretical grounds.

Hughes (1947) studying the action of B.A.L. on Lewisite burns of the eyes of rabbits, found that a single instillation of 5% dimercaprol solution or ointment from within two to five mintues after exposure to Lewisite,

effectively prevents the development of serious ocular lesions. He holds that this effect of dimercaprol is due, in part at least, to its rapid penetration and withdrawal of toxic arsenical material from the tissues before irreversible histological changes have developed.

(2) Treatment of Mustard Gas Lesions.

Hughes (1942) has summarized the methods available in mustard gas injuries of the eye. He mentions the importance of reassuring the patient that he is not blind in the early stages by opening the lids, and warns against the use of local anaesthetics which may damage the corneal epithelium. Dealing with treatment by irrigation the author does not discriminate between vapour injuries and splash injuries, but advises immediate irrigation of the eye as being applicable to all cases. Irrigation is now considered to have no value and may even be harmful if applied in the presence of an established lesion (e.g. vapour cases at the onset of symptoms), but on the other hand immediate and thorough irrigation may save the eye after a splash injury. The use of a mydriatic is advocated by the author in cases with corneal or iris involvement and in certain cases where photophobia is troublesome. The eye should not be covered although the temporary use of dark glasses or a shade is permissible. Bland oily drops and mild antiseptics are recommended in the later treatment.

Scherling and Blondis (1944) have reported on the treatment of mustard gas injuries to the human eye in eighteen cases, one of which was caused by a splash of

liquid mustard. Most cases were given homatropine to eliminate photophobia and spasm, and in the first few days a solution of epinephrine hydrochloride (8% of 1:1000) and camphor water (4%) in distilled water was used frequently. The use of glycerine was recommended to combat the corneal oedema that accompanies mustard gas kerato-conjunctivitis. Unfortunately the evidence in this paper is insufficient to indicate whether these substances have any particular therapeutic value in mustard gas burns of the eye. The vapour cases had all cleared up in from two to fourteen days as would be expected in mild cases having bland treatment, while the splash case still showed signs of recurrent keratitis more than three months after the injury.

Mann (1944) reviewed the subject of treatment of delayed mustard gas keratitis in a series of eighty-four cases. All were fitted with contact lenses. The visual acuity in all but two cases was markedly improved. In twenty-five cases there was no further relapse after fitting, and in ten only were severe relapses encountered. In relapsing cases shallow ulcers responded well to mydriatics and heat, while in deeper ulcers accompanied by discharge of cholesterin and fatty debris, gentle curettage followed by tarsorrhaphy was undertaken. Raised superficial corneal plaques were scraped off before fitting a contact lens. When stasis was encountered in varicose vessels of blood islands, the blood was evacuated by pricking, or feeding vessels were dealt with by cautery or peritomy.

Scholz and Woods (1947) found 243 cases of

relapsing and chronic ocular lesions following mustard gas burns in a review of the literature. From examination of the report of 136 cases in which the data were sufficient, these authors concluded that while no universally beneficial treatment has been recorded the use of contact glasses to promote healing of recurrent ulcers and to improve vision has been the most successful method.

No literature has been published so far on the treatment of ocular lesions due to nitrogen mustard gas.

(3) Treatment of Lesions due to Inorganic Chemicals.

It has been found experimentally that acid burns of the eye result in early protein precipitation and a non-progressive lesion, and that the prognosis is relatively good unless contamination is very severe. In the case of alkali burns, however, the lesion tends to be progressive. Hughes (1946) has reviewed the available methods of treatment for the latter and finds that conservative treatment is effective for alkali burns of mild or moderate severity. This consists of:-

1. Immediate irrigation of the eye with copious amounts of water or any bland solution.
2. Removal of any residual particles of alkali from the conjunctival sac and instillation of buffer solution. (pH 4.5)
3. Instillation of mydriatics.
4. A corneal bath of 10% neutral ammonium tartrate after lime burns.
5. Sulphonamide or Penicillin ointments to prevent secondary infection.
6. Prevention of symblepharon.

Early and repeated paracentesis may be beneficial but the number of reported cases is small. Hughes found that the evidence in favour of early excision of necrotic conjunctiva with replacement by membrane grafts was inconclusive.

Scherling and Blondis (1944) describe a case of ocular burns from white phosporus and report favourably on treatment by 3% solution of copper sulphate. After free irrigation of the eye using boric acid solution, a local anaesthetic was instilled, followed by repeated applications of a few drops of the copper sulphate solution over a period of fifteen minutes.

PART 3.

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PART 4.

"By this way of Analysis we may proceed from Compounds to Ingredients, and from Mȯtions to the Forces producing them; and in general, from Effects to their Causes, and from particular Causes to more general ones, till the Argument end in the most general."

Sir Isaac Newton, Opticks, 1730.

PART 4.

CONTENTS.

A DISCUSSION OF OCULAR BURNS.

PART 4.

A DISCUSSION OF OCULAR BURNS.

1. Introduction.

The term burn is used to designate a series of pathological changes set up in the tissues as a result of external interference by certain chemical or physical agents. The complete sequence of events by which these changes take place is still far from being fully understood, but an attempt can be made to form an intelligible picture of the processes involved in certain instances. The clinical and pathological appearances of the gross lesions have been established by several obsefvers and provide a firm frame of reference for theoretical interpretation. The sciences of chemistry and physics are continually being brought into closer association with each other, with increasing appreciation of the scope of application of their respective fundamental theories. There exists, however, a great gap in knowledge between physico-chemical theory and the morbid anatomy of biological processes. The slit-lamp enables us to fumble at the upper end of the gap by observing the development of pathological lesions in transparent living tissues such as the cornea, while biophysics and biochemistry are being brought to bear on the other end of the gap in an attempt to elucidate biological processes by the application of physico-chemical methods and theory. But the gap is still wide as will appear from further contemplation on the

interpretation of these studies in the ocular reaction to certain irritants.

2. Statistical Considerations.

The analysis presented in Part 1 shows that 94 cases of ocular effects resulting from burns occurred amongst 14,234 ophthalmic cases. These 94 cases could be divided into two groups:-

I. 87 cases of recent injury to the region of the eye.

II. 7 cases of ocular complications of burns.

The proportional rate of occurrence of recent burns of the eye amongst a hospital population was found to be 0.67%. The majority of such injuries occurred during the years of life usually occupied in gainful employment, but there was a significant difference in the age distribution with regard to sex in that no females were found in age groups over 40 years of age.

The agents involved in the causation of these recent injuries could be divided roughly into four groups with the following frequency distribution:-

1. Chemical..... 45
2. Thermal..... 35
3. Combined Chemical and Thermal.. 3
4. Radiational..... 4

It was shown that there was a significant association between the unilateral or bilateral character of the injuries and the nature of the injuring agent. In particular, an association was found between the physical

state of the agent and the laterality of the resulting injury, since solids and liquids tended to cause a unilateral lesion while the vapour state favoured the production of a bilateral lesion.

Out of 53 cases in which the records of visual acuity were sufficient for analysis, 13 cases had defective vision prior to the injury, 37 recovered adequate vision (better than 6/12 in each eye) while in 3 cases only could the defective vision be attributed definitely to the injury. Permanent structural damage to the eye as a result of the injury was observed in 6 cases only.

When the cases were divided according to the number of days of in-patient treatment or the number of days of out-patient attendance, the observations fell into series distributions. The severity of these injuries based on the number of days spent at hospital for treatment was found to be associated significantly with the character of the ocular injury with regard to the region affected. Corneal involvement was associated with a significant increase in the severity.

In other respects the data were of interest on account of negative findings. There was no evidence that the frequency of occurrence of ocular burns was affected during the war years in the population under investigation. The data contained no evidence of association between the age of the patients and the severity of the injuries, nor between sex and severity. Again, there was no evidence of a significant difference in severity between acid and alkali

burns, such as is commonly believed to exist.

The cases of ocular complications of burns have already been discussed in Part 1.

3. Physical Considerations.

It is known with regard to lethal gases that the biological effect produced is roughly proportional to the product of the concentration of the gas (C) and the time of exposure (T). In the case of mustard gas vapour acting on the human eye it has been found by experiment that the dosage required to produce threshold effects is relatively constant in terms of CT. expressed in mg. min./ cub. metre. In dealing with clouds of fine droplets of the order of 100 μ and less in diameter, however, it may be expedient to express the degree of contamination in terms of area dosage (gm./ sq. metre). In using larger drops the dosage is conveniently expressed in terms of the drop diameter.

In the course of the experimental work described in Part 2 an impression was gained that the severity of the lesion in the eye depended less on the actual weight of chemical substance applied to the eye than on the physical state, and, in particular, the droplet size in which it was presented. For instance, either mustard gas or nitrogen mustard gas applied as 32 drops of 150 μ in diameter (total dose in eye = 0.064 mg.) produced a much more severe reaction in rabbits than the same substances applied in the form of drops of less than 100 μ diameter with 50% of the mass being of the order of 40 μ in diameter (total dose in eye = 0.06 mg.).

It is known that in the case of lacrimator substances the hazard to the eye (aggressiveness) from a particular substance in vapour form depends not only upon the activity of the substance but also on its vapour pressure. In the study of certain nitrogen mustard compounds which constituted a homologous series it was observed that the relative aggressiveness of these substances in the form of vapour decreased more rapidly with increasing molecular weight than their activity in the eye.

The viscosity of substances applied to the eye also appears to have an important bearing on their activity. Solutions of identical strength w/v of mustard gas prepared using several grades of liquid paraffin which varied in viscosity and density were found to produce lesions differing greatly in severity. The more viscous paraffin solutions produced the more severe and more constant lesions, presumably because they retained the solute in contact with the eye for a longer time. This same effect was observed using B.A.L. ointments. B.A.L. has eye irritant properties. When applied to the eye in large excess in a lanolin base, the lanolin melts in contact with the tissues and any excess flows away, so that ocular irritation caused by prolonged contact with B.A.L. is minimal. When an equal weight of B.A.L. is applied in a similar quantity of a lanette wax base, the ointment remains solid in contact with the eye and produces considerably more ocular irritation.

4. Chemical Considerations.

It has been shown that substances within the

chemical group could be differentiated to some extent by means of the effects they produce in the ocular tissues and it is now convenient to obtain some conception of the chemical nature of these compounds in order to ascertain whether there is any evidence of correlation between chemical structure and activity in the eye.

Organic chemical substances all contain the elements carbon (C) and hydrogen (H). Some contain oxygen (O), nitrogen (N), the halogens- fluorine (F), chlorine (Cl), bromine (Br), the iodine (I) - sulphur (S), phosphorus (P) and arsenic (As). The hydrocarbons - compounds of hydrogen and carbon - constitute the simplest group of organic compounds, and methane (CH_4) is the simplest member of this group. Removal of one hydrogen atom from methane leaves the methyl radicle (CH_3) - or in general terms, an alkyl radicle. Methane is the simplest member of the paraffin series, in which there is a difference of CH_2 between consecutive members. This is termed homology.

Homologous Series.		Alkyl Radicles.
Methane CH_4	or	CH_3 - H
Ethane C_2H_6		C_2H_5- H
Propane C_3H_8		C_3H_7 - H
Butane C_4H_{10}		C_4H_9 - H

The arsenical substances discussed in Part 2 were all trivalent. Organic arsines may be regarded as being derived from arsine (AsH_3) by substitution of alkyl groups in place of the hydrogen atoms. Primary, secondary, or tertiary arsines are formed according to whether one, two, or

all three hydrogen atoms are replaced. They can be represented by the following general formulae:-

Primary arsines.	$RAsX_2$
Secondary arsines.	R_2AsX
Tertiary arsines.	R_3As

The nitrogen mustard substances may be thought of as substituted ammonias, where the hydrogen atoms in ammonia (NH_3) are replaced by various alkyl groups to form amines. Amines may also exist in primary, secondary, or tertiary form:-

Methylamine.	$CH_3 - NH_2$	(primary)
Dimethylamine.	$(CH_3)_2 = NH$	(secondary)
Trimethylamine.	$(CH_3)_3 \equiv N$	(tertiary)

Secondary amines react with nitrous acid to form nitrosamines as seen in the reaction:-

$$\begin{matrix} R \\ R_1 \end{matrix}\!\!>\!NH + HO - NO \longrightarrow \begin{matrix} R \\ R_1 \end{matrix}\!\!>\!N - N = O + H_2O$$

Nitrosamine.

Nitrogen mustard (ββdichlor diethyl methylamine) may be regarded as a tertiary amine where two hydrogen atoms have been replaced by chloroethyl groups and the other by a methyl radicle:-

$$H - N\!<\!\begin{matrix} H \\ H \end{matrix} \longrightarrow CH_3 - N\!<\!\begin{matrix} CH_2CH_2Cl \\ CH_2CH_2Cl \end{matrix}$$

Ammonia. Nitrogen Mustard.

The structure of mustard gas may be conceived simply in the following way:-

Water. $H - O - H$

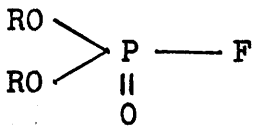
Alcohol. $C_2H_5 - O - H$ (alkyl hydroxide)

Ether. $C_2H_5 - O - C_2H_5$ (alkyl oxide)

Thio-ether. $C_2H_5 - S - C_2H_5$ (alkyl sulphide)

Mustard gas. $S(CH_2CH_2Cl)_2$

The fluorophosphonates are substances of general formula:-



Amongst therapeutic substances B.A.L.(British Anti-Lewisite) was of outstanding interest. This compound is a dithiol and its derivation can be easily followed beginning with Alcohol:-

Alcohol R - OH

The substitution of S for O gives a mercaptan:-

Mercaptan R - SH

Mercaptans are substances having an affinity for mercury, and the hydrogen atom may be replaced by mercury and certain other metals including arsenic. The thiol group - SH can also occur by substitution in dihydric alcohols:-

Glycol $\begin{matrix} CH_2 - OH \\ | \\ CH_2 - OH \end{matrix} \longrightarrow \begin{matrix} CH_2 - SH \\ | \\ CH_2 - SH \end{matrix}$ (a simple dithiol)

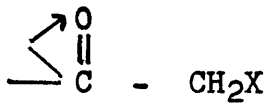
B.A.L. or dimercapto propanol is a dithiol preparation selected on account of its ability to penetrate the tissues:-

B.A.L. $\begin{matrix} H_2C - SH \\ | \\ H - C - SH \\ | \\ H_2C - OH \end{matrix}$

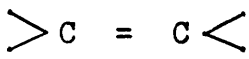
5. Chemical Structure and Activity in the Eye.

In the case of substances having lacrimatory properties it has been possible to correlate lacrimatory activity with chemical structures (Ford, Moore, 1936). These properties have been found to depend on the presence in the molecule of either:-

(a) a positive halogen, e.g.



or (b) an olefinic linkage, e.g.



It has been suggested (Needham and Dixon, 1946) that the same groups (ketone, ester, aldehyde, etc.,) which give the neighbouring halogen its positive properties also polarize adjacent olefinic linkages so enabling them to act as lacrimators.

With vesicant substances in general, however, it has not been possible to correlate chemical structure with activity. At the same time certain observations on this aspect of the subject are worthy of note. Substances of the lacrimator group have been found to cause structural damage in the eye when applied in sufficient dosage, and in this respect they resemble the vesicant substances. Of the arsenical substances examined for activity in the eye, primary arsines of general formula $RAsCl_2$ were known to have a vesicant action on the skin; secondary arsines, R_2AsX, were known to have sensory irritant properties, but activity had not previously been demonstrated for tertiary arsines,

R_3As. Arsenical analogues of nitrogen mustard gas (ββdichlor diethyl methylamine) which were also tertiary arsines were found to be capable of causing injury to the eye. The lesion produced, however, was of arsenical type and did not have the characteristic features of injury by nitrogen mustard gas. In a group of four primary arsines activity was found to decrease in the order:-

βChlorovinyl dichlorarsine.
Phenyl dichlorarsine.
Methyl dichlorarsine.
Ethyl dichlorarsine.

The main features of the arsenical group may therefore be summarised as follows:-

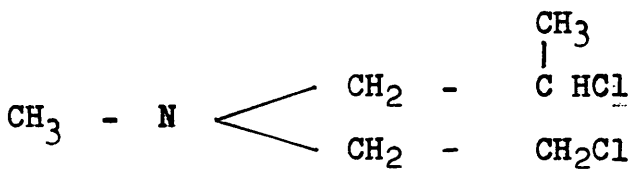
1. All trivalent arsenical substances which were examined, whether primary, secondary, or tertiary compounds were found to produce structural damage in the eye.

2. The arsenic atom appeared to have an over-riding influence in determining the clinical type of lesion, since arsenical analogues of nitrogen mustard gas produced an ocular lesion of arsenical type.

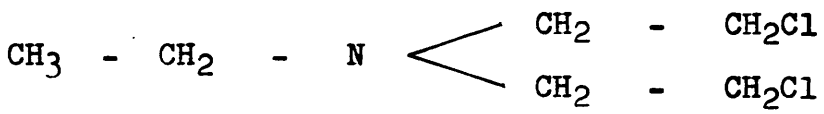
N carbomethoxy βchloroethyl nitrosamine proved to be the most potent substance in the nitrosamine group. The bromo-analogue, N carbomethoxy βbromoethyl nitrosamine was found to be similar in action on the eye and possessed a high order of activity. N carbomethoxy β(βchloroethylβthio) ethyl nitrosamine contains structural groups of both nitrosamine and mustard gas in the molecule and was found to possess a high order of activity. In contrast, the parent substance of this series of compounds, N carbomethoxy methyl nitrosamine is almost devoid of eye injurant

properties so that a β chloroethyl group is an essential factor in originating aggressiveness. Again β chloroethyl methyl nitrosamine and di (β chloroethyl) nitrosamine are not eye injurants, so that the presence of the ester grouping (- COOR) also seems to be necessary.

The activity of homologues of β/β dichlor diethyl methylamine (nitrogen mustard) rapidly disappears as the molecular weight increases. This is true both for introducing methyl groups into the β chloroethyl groups:- e.g.



and into the third alkyl group:- e.g.



Decrease in power of producing eye injuries was found roughly to correspond to decrease in vesicancy. To produce either effect the presence of the β chloroethyl groups seems to be essential since β chloroethyl dimethylamine and β chloroethyl morpholine are both inactive. Replacement of one of the β chloroethyl groups by groups like CN, - $COOCH_3$, - NO, or Cl does not enhance the power of these amines to produce ocular injury, but in comparison the presence of a third β chloroethyl group in trichlortriethylamine does lead to the production of an active though not outstandingly potent substance.

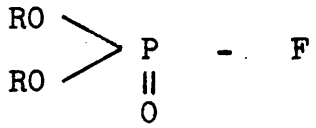
The nitrogen mustard type of lesion was produced only by β/β dichlor diethyl methylamine and its ethylhomologue

although a similar ocular lesion was obtained by injury with certain of the hydrolysis products of ββdichlor diethyl methylamine.

Only a few homologues and analogues of mustard gas were examined. Of these 22 di (βchloroethyl thio) diethyl ether was found to be much less active in the eye than mustard gas, while ββdichlor diethyl sulphone was apparently inert.

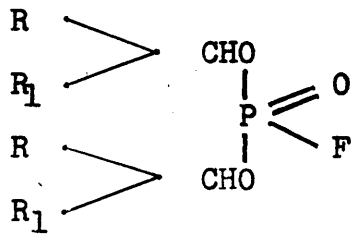
From these observations it can be seen that there is no evidence of any firm correlation between the chemical structure of these vesicant substances and their ability to injure the eye.

McCombie and Saunders (1946) found an example of strict correlation between chemical structure and activity in the case of the fluorophosphonates. It will be remembered that these substances can be pepresented by the general formula:-



They have a pronounced miotic action in the eye and a high toxicity when absorbed systemically. If the R is isopropyl or sec. butyl in the above formula the toxicity is of a higher order than with a primary group such as R = ethyl, n-propyl, n-amyl, or iso-amyl. The miotic effect and toxicity become negligible when the fluorine atom is replaced by other atoms or groups. These effects also disappear when oxygen atoms are replaced by sulphur, while ethyl di-fluorophosphonate is found to have neither a miotic

nor a toxic effect. On the other hand a secondary grouping:- e.g.



increased the potency.

6. The Mode of Action of the Agents.

While the mode of action whereby chemical substances bring about their poisonous effect in the body tissue is still largely unknown, recent advances in biochemical knowledge appear to reveal the principles underlying the action in some instances. Various workers in the biochemical field have agreed that it is probable that many poisonous chemical substances act by attacking one or more of the essential intracellular enzymes producing a "biochemical lesion". Studying the war gases, Dixon and Needham (1946) found that:-

1. Different classes of substance (lacrimators, vesicants, miotics,etc.) do in fact poison different groups of enzymes.

2. Different substances of the same class, although having very different chemical constitutions, in general poison the same enzymes.

These observations were considered to give very strong support to the view that poisons act primarily by a specific attack on enzymes.

(1) Lacrimator Substances.

Dixon and Needham show that lacrimator substances

irreversibly inhibited all those enzymes the activity of which had already been shown by independent evidence to depend on - SH groups. A large number of other enzymes were not affected. Only the reduced - SH form was inhibited, and not the oxidised - SS form, but the nature of the connection between the - SH groups in the nerve endings and the production of a nervous impulse is not known. Lacrimators were also found strongly to inhibit cell respiration and glycolysis.

(2) Vesicant Substances.

a. Arsenical Substances.

Preliminary work on aneurin deficiency (Peters, 1940) established that serious pathological changes could result in the brain from partial failure of an enzyme system such as the 'pyruvate oxidase' system. Pursuing this idea it was conceived that the activity of arsenical substances was due to a selective action on some essential - SH component of the pyruvate enzyme system (Peters, Stocken and Thompson, 1945). Later work led to the reasoning that the high toxicity of trivalent arsenicals was due to their ability to combine with essential - SH groups in certain tissue proteins, notably enzymes, to form stable arsenical rings. It was found by the same observers that the arsenic content in a tissue treated with an arsenical substance could be correlated closely with the thiol content of the parent protein and that the greater part of the arsenic was in combination with two thiol groups in the tissues. It seemed likely that simple dithiol compounds might form relatively

stable ring compounds with trivalent arsenicals and so compete successfully with "dithiol" proteins in the tissues. This proved to be the case and after a number of dithiols had been tried, a new compound B.A.L. (2 : 3 dimercapto-propanol) was prepared (Peters, Stocken and Thompson) which had superior powers of penetration.

Trivalent arsenicals have a strong inhibitory action on certain - SH enzymes by combining with - SH groups, but this action on - SH enzymes differs from that of the lacrimator substances (Dixon and Needham,1946) in that it is reversible, and since not all of those enzymes which are poisoned by lacrimators are significantly affected by arsenicals. The degree of inhibition is correlated with the affinity of the enzyme for the arsenical.

The dithiol antidote B.A.L. was found to counter-act the effects of the arsenical poisoning if used within a certain time of the injury. It is even claimed (Peters, Stocken and Thompson, 1945) that the antidote will reverse a pathological change in the tissues resulting from the enzyme deficiency caused by arsenic. This claim appears to be based on the observation that in some cases of Lewisite skin burns the subsidence of the skin oedema following treatment by B.A.L. "was sufficiently rapid to suggest an actual reversal of the underlying pathological change brought about by the Lewisite". With regard to arsenical burns of the cornea, however, it will be remembered that Hughes (1947) demonstrated two components in the Lewisite burn; one causing immediate corneal opacification and thought to be due to the formation of hydrochloric acid in the tissues as a result of

hydrolysis; and later changes due to the arsenical group in the molecule, changes which could also be produced by intra-corneal injection of neutral Lewisite oxide solution. He found that there was evidence of irreversible pathological changes in the cornea beginning ten minutes after exposure to the arsenical.

On the available evidence I am hesitant to subscribe to the idea that B.A.L. will reverse an established pathological change. It seems more probable that the arsenical lesion is made up of two components, one due to acid which is recoverable and a second due to arsenic which can be prevented by the timely use of the antidote. There can be little doubt, however, that arsenical substances act in the tissues by causing an enzyme block or partial enzyme deficiency.

b. Nitrogen Mustard Substances.

Little is known so far of the biochemistry of the nitrogen mustard compounds. They are effective inhibitors of cholinesterase (Dixon and Needham, 1946), but they are also responsible for other enzyme inhibitions and it is not yet possible to come to any conclusion from biochemical studies as to their mode of action.

c. Mustard Gas.

Although extensive biochemical investigations have been undertaken to determine the mode of action of mustard gas in the tissues, it is very significant that no satisfactory advance in knowledge has been achieved by this approach as in the case of arsenicals. Dixon and Needham,

(1946) contend that a biochemical lesion may also be involved in the case of mustard gas, in that they have found that mustard causes inhibition of glycolysis due to poisoning of hexokinase, an enzyme concerned with the initial phosphorylation of glucose. Peters, (1947) points out, however, that it is difficult to reconcile this theory with cumulative histological evidence that mustard gas makes an immediate attack upon the skin. He contends that the first attack of this poison may be upon the cell surface with resulting alteration in permeability and a contingent dilution of cell constituents.

Auerbach and Robson (1946) made the interesting observation that certain chemical substances are as effective as X-rays in inducing mutations and chromosome rearrangements. They claim this property for mustard gas and other compounds chemically related to mustard gas, while they found that Lewisite gave negative results. They contend that "the mutagenic action of mustard gas appears to be exercised directly on the chromosomes and not by way of a change occurring primarily in the cytoplasm; for the mutation rate is not increased in untreated spermatozoa which have been introduced into treated eggs". Various rearrangements (inversions, large deletions, translocations) were produced by the treatment. In a further contribution to the literature (1946) these authors stress that this drastic action on the cell nucleus will be observed essentially in tissues which are still actively dividing.

Berenblaum and Schoental (1947) found that

mustard gas had a rapid and powerful action on nucleoprotein causing irreversible precipitation; this is noteworthy in view of the mutagenic action of the poison described by Auerbach and Robson.

(3) Miotics.

Alkyl fluorophosphonates were found (Dixon and Needham, 1946) to resemble eserine in that they are powerful inhibitors of choline esterase (so allowing the action of acetyl choline to proceed unhindered at the third nerve endings in the sphincter iridis) but they differ from eserine in that the inhibition of choliha esterase is progressive and irreversible. These substances are highly specific in action, affecting only the esterases, and are the most powerful enzyme inhibitors known, an account of the extremely low concentration at which they are effective.

(4) Inorganic Substances.

Inorganic substances are usually of interest on account of their acid or alkaline properties, as far as their action on the eye is concerned.

Friedenwald, Hughes and Hermann (1946), suggest that the clinical and pathological characteristics of acid burns of the cornea may be explained by precipitation and denaturation of the proteins of the cornea. They found that the severity of the corneal lesion produced by acids was directly related to the protein affinity of the anion. Anions with greater affinity for proteins (e.g. picric, tungstic, and tannic acids) produced corneal lesions at a higher pH than anions with lesser protein affinity (e.g.

hydrochloric, trichloracetic, and metaphosphoric acids.) but the maximum lesion produced by any one of these acids was essentially the same. They therefore related the clinical reactions to the formation of protein-anion combinations, and since the tissue damage was not reversed by return of the pH to normal concluded that the corneal proteins had been irreversibly changed.

Hughes (1946) found that the severity of the lesion in alkali burns was not greatly influenced by the type of cation, but considered that it depended more on the concentration of alkali, the duration of exposure, the pH of the solution and its penetrability.

It would appear from these observations that there is a fundamental difference between acid and alkali burns but the details of the biochemical processes involved are not known.

(5) Burns due to Heat and Radiations.

The ultimate result of a severe thermal burn of the ocular tissues appears to be a coagulation necrosis. When a naked flame or an incandescent object comes in contact with the cornea rapid opacification results from coagulation of the tissues. The changes involved are presumably of a biophysical nature and the processes can be conceived theoretically more easily than they can be studied experimentally.

When radiational agents are considered one realises that they form a heterogeneous class. Before radiations can undergo the energy conversion necessary to

produce a lesion they must be absorbed by the tissues. Certain radiations after absorption are found to cause a thermal lesion, others alter the chemical nature of the constituent atoms of the tissues producing a chemical or abiotic lesion, while others again appear to produce their biological effects by causing ionization in the tissues. Further, biologically active radiations are known to produce an increase in the rate of mutation of genes, the hereditary units carried by the nuclear chromosomes, and Stuhlmann(1943) states that "genetic changes occur in direct proportion to the dose of radiation and are independent of its wave length".

7. Clinical Considerations.

It is now proposed briefly to consider a few points of general biological interest emerging from these studies.

(1) Vesicant Substances.

In a previous section the mode of action of arsenical substances has been discussed and it has been shown that biochemical methods reveal that arsenicals act by attacking essential - SH enzymes. The lesion produced in the eye is, therefore, the result of local enzyme deficiency.

The nature of the ocular injury resulting from nitrogen mustard has not been elucidated so far by biochemical studies. The course of this ocular lesion in the rabbit is very characteristic and conveys to the observer certain clear clinical impressions. There is a

latent interval before signs appear in the eye; the initial corneal reaction is severe but settles with remarkably little permanent scarring; there is acute iritis with haemorrhages into the stroma and paralysis of the musculature, and from the tenth day onwards gross haemorrhages occur from the iris and ciliary body - the whole reaction subsiding eventually leaving vitiligo iridis, and iris atrophy and deformity. This picture bears a close clinical resemblance to some cases of ocular infection with Herpes Zoster. It follows even more closely the course described by Loewenstein (1944) following experimental inoculation of the rabbit's eye with Herpes virus. Nitrogen mustard is known to have neurotropic properties, and in this it resembles certain strains of Herpes virus.

The action of mustard gas has not yet been adequately explained biochemically, although it has been extensively studied. Late corneal degeneration is a relatively rare but peculiar feature of this type of ocular injury, and Mann and Pullinger (1942) present the theory that this lipoidal degeneration is dependent on chemical injury followed by vascularization of the cornea. Their hypothesis is stated as follows:- "In the cornea, lipoid degeneration is the last event in a series of changes following chemical damage of various kinds. Let the chemical be called X. The chemical X does not itself cause these deposits for they never appear unless the cornea vascularizes, and then only occasionally. The vessels or something which accompanies them are responsible for the lipoid accumulation. Invasion

of the cornea by wandering cells alone does not account for the lipoid scars because all central non-vascular lesions heal with the aid of wandering cells, but deposition of lipoid is never a feature of these scars".

Two of the cases described in Part 1 of this thesis are of particular interest in that they show late corneal degeneration as a result of mustard gas without evidence of any corneal vascularization. (Serial Nos. 92 and 94). The first case, No. 92, gave a typical history of a severe mustard gas injury to the eyes which was followed after an interval of 21 years by corneal dystrophy. The type of dystrophy was consistent with a diagnosis of late corneal degeneration due to mustard gas, and this diagnosis was supported by collateral evidence of mustard gas poisoning. There was no evidence, however, of any corneal vascularization in either eye, nor was there evidence of any vascular abnormality in the conjunctiva. The second case, No. 94, also suffered severe ocular injury from mustard gas followed by late degeneration of the cornea. In this case the observer made special note of the relative absence of new vascularization of the tissues, and in particular mentioned that there was no evidence of deformed vessels or disused vascular channels in the cornea. Both these cases leave little doubt that the corneal dystrophy was caused by mustard gas; yet there is an absence of the vascularization of the cornea which Mann and Pullinger consider an essential process in the production of the dystrophy. These cases raise the question as to whether corneal vascularization is

essential to the production of the late degeneration or is merely a frequent concomitant in this form of dystrophy.

It has been mentioned above that Auerbach and Robson (1944) have shown that mustard gas and chemically related compounds are capable of inducing gene mutations and chromosome rearrangements, while Berenblaum and Schoental (1947) have demonstrated that mustard will cause selective precipitation in nucleo-protein. Since this action would be expected to become manifest in rapidly growing tissues it presents a reasonable explanation of certain of the features of the late dystrophy of mustard. The bizarre shapes and abnormal forms seen in rapidly growing new vessels, and the main impingment of the dystrophy at the level of the epithelium and Bowman's membrane are consistent with this interpretation of its action. Further there is no need to include corneal vascularization as an essential step in the production of the dystrophy on this hypothesis.

Thus it appears that of these three types of chemical substance, one acts by attacking essential enzymes to produce a local enzyme deficiency, the second reproduces many features resembling an ocular infection by a virus, whilst the third may act by producing a somatic mutation in a gene. Such a conclusion is of particular interest in view of the trend of modern biological opinion with respect to the possible associations existing between genes, enzymes, and viruses.

Pontecorvo (1946) reviews the recent work and puts forward a hypothesis relating genes, enzymes, and

viruses. It is known that each step in a chain of metabolic reactions may be controlled by a specific gene, and it has been suggested that gene reproduction and gene action may be considered as two complementary aspects of the same activity. There is evidence that the ability to produce an enzyme is generally inherited as a Mendelian dominant, and it seems that the control by genes of elementary biochemical steps takes place through enzymes. Pontocorvo contends hypothetically that specific genes may be responsible for the production of traces of the precursor substance of enzymes, and that such enzyme precursors may increase autocatalytically in the presence of the appropriate intra- or extra-cellular substrate. Such substances may increase independently of the genes, and in certain cases they may be transmitted externally from one cell to another, there causing disease, in which case they manifest the behaviour of viruses.

Certain viruses are known to be non-living protein molecules which are capable of increasing their number autocatalytically under suitable conditions, and there is evidence associating virus properties with the molecule of nucleoprotein.

Having such considerations in view it may not be without significance that chemical substances can invoke in the ocular tissues responses having the characteristics of (a) an enzyme deficiency, (b) a virus disease, or (c) a mutation of genes.

(2) Radiations.

It has already been mentioned that mutagenic

activity is a property common to mustard gas and related substances and to certain radiations. A case of degenerative changes in the ocular tissues (Serial No. 4) following X-ray therapy for carcinoma of the ethmoid sinus was included in Part 1. Little is known with regard to the course of such degenerative lesions caused by radiations and certain features of this case are noteworthy when regarded on the hypothesis that they are the result of mutagenic action. The dystrophy was observed in the ocular tissues in the following order with respect to time of appearance:-

1. Corneal epithelial dystrophy..... a few months.
2. Varicosity of conjunctival vessels and corneal vascularization..... 1 year.
3. Opacities in subcapsular region of lens..... 2 years.
4. Iris atrophy and depigmentation..... 4 years.

It is known that radiation must be absorbed to produce biological activity and that genetic changes occur in direct proportion to dosage and are most marked in actively growing tissues. The corneal epithelium and the epithelium of the lens are both actively growing tissues in young persons and this would account for the appearance of the dystrophy at these sites. It is probable that less radiation would be absorbed in the lens than at the corneal surface, and this factor together with difference in the rate of cell division in these epithelial structures might account for the difference in the rate of mutation with

corresponding difference in the time of appearance of the dystrophy in the two tissues. The appearance of varicosities in the conjunctival vessels is reminiscent of the action of mustard gas, a substance with mutagenic properties.

The iris tissue is not usually regarded as showing great activity in the matter of cell division, but it is a tissue containing a high proportion of pigmented cells. It is possible that the pigment content may increase the radiational absorption sufficiently to induce mutagenic activity although the rate of mutation may be only slightly increased owing to the relative absence of growth changes in the tissue, with resulting delay in the appearance of the dystrophy.

8. Theoretical Considerations.

Any attempt to form an intelligible picture of the processes involved in burns must begin with some elementary conception of the present theories with regard to the physics of matter and radiations.

(1) Matter and Radiations.

Matter is regarded by the physicist as being composed of atoms which may be grouped together into molecules. On the electronic theory of matter these atoms are considered to consist of minute positively charged nuclei surrounded by negative electrons, while the wave-mechanical treatment of the electrons in an atom regards the system as a complex of standing 'waves' of a vibrating quantity with an intricate arrangement of nodes. An atom can be thought of as

a nucleus surrounded by an electron cloud, the density of which at any point represents the probability of an electron being found there, and in chemistry, the electrons are regarded as being actually located in these regions of high density.

Electrons can exist at different levels in an atom as may be seen in atomic spectra. Similarly molecules can exist in different atomic states, and when they undergo electronic transition by absorption or emission they also undergo changes in their energies of vibration and rotation. Absorption of radiation produces a compressed, highly excited molecule, but to produce appreciable electronic excitation by heat alone requires exceedingly high temperatures.

The electro-magnetic theory of Maxwell considers the 'waves' of radiation to be of the nature of alternating currents with their associated magnetic effects. The electric displacements of the waves are imagined as interacting with electrons or nuclei to produce the effects of radiations on matter, but phenomena involving the absorption of radiation need the additional assumption of the Quantum Theory which implies that energy in the form of radiation is absorbed in quanta of specific magnitude. Radiation appears therefore to have a dual nature, that represented by electro-magnetic waves and that more like the concept of a particle or bundle of energy of fixed amount.

The principal radiations can be divided into two groups, corpuscular and electro-magnetic (Rochester, 1944).

The corpuscular radiations include alpha particles, beta particles and neutrons: while the electro-magnetic radiations include gammarays, X-rays, ultra-violet radiation, visible radiation, and infra-red rays. Corpuscular radiations are emitted in the natural or artificial disintegration of atomic nuclei. Alpha particles - positively changed helium nuclei - are emitted by naturally radio-active substances like radium, but have little penetration because they dissipate energy rapidly by formation of ions; beta particles are high-speed electrons ejected from radio-active nuclei or from the outer electron shells by gamma rays - they lose less energy by ionization and have correspondingly greater penetration; neutrons are neutral particles produced when certain elements are bombarded by alpha particles - they have a very great range because their ionization loss in matter is extremely small. All the electro-magnetic radiations travel with the same velocity as that of light, and differ only in wave-length. Gamma radiation is the shortest known electro-magnetic radiation (frequency 10^{19} - 10^{20} per sec.); it is emitted by radio-active nuclei and arises from changes in the energy levels in the nucleus of the atom, thus involving atomic transformations; penetration is very great, and energy is lost by production of beta particles - photo-electrons ejected from the outer shells of atoms - and by scattering in matter. X-rays (frequency 10^{16} - 10^{18} per sec.) arise from the inner electron shells of atoms, and lose energy by the production of photo-electrons and by

scattering. Ultra-violet and visible radiations (frequency about 10^{15} per sec.) arise from electrons in the outer shells of atoms and molecules, regions concerned with chemical changes. Near infra-red rays (frequency 10^{13} - 10^{14} per sec.) result from the vibrations of atoms bound together as molecules, while far infra-red rays (frequency 10^{12} - 10^{13} per sec.) are a product of the rotations of the molecules.

Considering now the effects of radiation upon matter, an electro-magnetic wave may be conceived to produce a distortion of the electrical structure of the atom or molecule by induction. The electrons, atoms, and molecules in matter are bound together by electrical attractions by virtue of which they have 'natural periods' of vibration. If the periodicity of the incident radiation is very close to a natural period of the matter, forced vibrations are induced. When certain natural periods are excited the energy is rapidly converted into other forms; it may become chemical energy by dissociation of the molecule or heat energy by conversion into vibrational or rotational energies. The radiation is absorbed in this way.

These theories make it possible to conceive of matter as being in continuous restless motion. High temperature increases the translational, vibratory, and rotational movements of atoms and molecules in a material; if such a heated material is brought into contact with another substance it will induce similar kinetic changes in the atoms and molecules of the second substance. Similarly the radiations produced by these movements in a heated

material can be envisaged to set up like movements in the atoms and molecules of substances into which they pass. Thermal changes can be imagined to arise in these ways.

(2) The Physical Interpretation of Chemical Bonds.

The movements of atoms and molecules are to some extent controlled by physical forces exerted by adjacent atoms and molecules. Certain atoms have the power to combine together and to this phenomenon has been given the name 'valency'. The fundamental principles of valency have been expressed very clearly by Speakman (1943) as follows:-

1. Chemical combination is due to the tendency exhibited by the extra-nuclear electrons of the atoms to reach certain stable groupings; these groupings are often, though not always, those existing in the inert gases.

2. The tendency may be satisfied by the complete transference of electrons from one atom to another, the resulting ions being held together by electro-static attraction and the process being called electro-valency.

3. The tendency may also be satisfied by a sharing of pairs of electrons between two atoms, which are thereby united by what is called covalency.

This bonding power is regarded as being located mainly in the outer electron shells of atoms and molecules. Disturbances in the electrons at this level produce actinic radiations which, in turn, may be conceived to act at the bonding level in the absorbing substances. Similarly chemical changes are considered to be derived from

disturbances of the arrangement of electrons in the outer atomic shells.

(3) The Biological Effects.

In the case of the ocular tissues the ultimate result of a severe burn, whatever the cause, appears to be a coagulation necrosis. When a naked flame or an incandescent object comes in contact with the cornea rapid opacification results from the tissue coagulation. This can be understood on a theoretical basis in that high temperatures produce compressed, highly excited electronic systems in the molecule which may result in agglutination of the proteins.

Apart from contact burns, however, a thermal lesion may result from absorption of radiation. "The periodicity of the longer wave-lengths - the infra-red - may be conceived as corresponding in a general way with the movements of the atoms. They are thus absorbed into this periodic system, and their energy finds expression in an increased rate of atomic movement, a phenomenon which is appreciated as heat, and which ultimately results in a coagulation of the protein of the tissue, thus causing a thermal lesion. The radiations of intermediate wave-lenths - the visible rays - finding no sympathetic resonator, as it were, slip through the transparent media without exerting any effect until the retina is reached. The shorter ones - the ultra-violet - whose frequencies correspond to the intra-atomic periodic oscillations are again absorbed. The energy they represent is added to

the atomic system so that the electrons are made to change their orbit, thus altering the chemical nature of the atom, or are jerked out of the atomic system altogether thus producing a photo-electric effect; this results ultimately in coagulation of the proteins, and the production of an abiotic lesion. Both these effects, the thermal and the chemical are quite distinct, although in the last instance they are identical, and are dependent on the transference of energy to the molecules or their parts, with the result that they are shaken apart". (Duke-Elder, 1932). Thus a chemical lesion, like a thermal lesion, may be initiated by radiations.

Interactions between chemical substances involve disturbances in the outer electron shells of atoms and molecules, and can be conceived to produce a chemical lesion by impinging on the periodic systems in the tissues at the same level as ultra-violet radiation.

When it is attempted to construct an intelligible conception of the action of radiations of still shorter wave-length - X-rays and gamma rays - interpretation becomes more difficult. Absorption of energy is necessary to produce a biological effect, and it is known in the case of X-rays that longer wave-lenths are absorbed much more readily than short waves in passing through matter. X-radiation corresponds in periodicity with the inner electron shells of atoms and is known to lose energy by absorption into this level with the ejection of planetary or photo-electrons. Further energy loss

occurs by scattering of the primary radiation and by Compton scattering - an effect due to the collision between a quantum of X-radiation and an electron. The resulting electron movements cause intensive ionization in the tissues, upon which process the biological action of the radiation is considered to depend. Absorption of gamma radiation causes changes in energy levels in the nucleus of atoms with ejection of beta particles, or high-speed photo-electrons which cause ionization along their paths through the tissues. These ionizing radiations appear to exert their effects preferentially on actively generating cells and cause an increase in the rate of mutation of genes. Stuhlmann (1943) states that "from the experimental evidence available one may conclude that absorbed photons in the form of X-rays or gamma rays for equal ionization doses produce equal effects". Genetic changes occur in direct proportion to the dose of radiation and are independent of its wave-length.

Apart from the ionizing effect of beta rays, corpuscular radiation is not of outstanding importance in relation to the present subject.

(4) Classifaction of the Burning Agents.

In the analysis of cases contained in Part 1 the agents responsible for these injuries were arranged into three main groups, (a) chemical, (b) thermal, and (c) radiational. A more accurate and detailed classification can now be formulated in the light of

the above discussion.

Classification.

1. Thermal Agents.
   (a) Contact with flame or materials at high temperature.
   (b) Infra-red radiation.
2. Chemical Agents.
   (a) Chemical substances.
   (b) Ultra-violet radiation.
3. Ionizing Radiations.
   (a) X-radiation.
   (b) Gamma radiation.
   (c) Beta radiation.

9. Conclusions.

Certain associations and conceptions have emerged from this survey of ocular burns based on an analysis of hospital data, an experimental study of chemical substances, a review of the literature, and a discussion of the biological effects.

Chemical substances may invoke in the ocular tissues responses which have the characteristics of an enzyme deficiency, a virus disease, and a somatic mutation of genes. A case of ocular injury by X-radiation has also been included on the hypothesis that the biological effects may be due to a mutation effect.

The actions of the various burning agents have been interpreted in theoretical terms and a classification

of the agents has been formulated.

It appears that the biological effects of ionizing radiations may become manifest in the form of a mutation. This occurs in direct proportion to the ionization dose but is independent of the wave-length. Genes are considered to be located in the nuclear chromosomes and are thought to consist largely of nucleo-protein.

While ultra-violet light resembles other ionizing radiations in possessing mutagenic activity, it is also known to produce abiotic changes in the tissues. Its absorption is considered to cause electronic disturbances at the bonding level in atoms and molecules which result in pathological changes, and in this respect its action is analogous to the interaction between chemical substances.

Three of the chemical substances studied were worthy of special comment on account of their biological effects.

Mustard gas and related chemical substances are known to cause selective precipitation of nucleo-protein and to produce mutation effects. It has been suggested that certain features of the ocular lesion caused by this substance can be interpreted in terms of a somatic mutation.

Nitrogen mustard gas has been shown to produce a lesion in the eye resembling a virus infection.

Genes and viruses are known to have certain points of similarity. Both have the power of self-duplication under suitable conditions in the living cell, a power which

need not imply a vital process since it can be interpreted by physico-chemical theory as a manifestation of mesomerism. Both genes and viruses may undergo mutations to forms having different biological activities but which retain this power of self-duplication. Also, since several viruses are known to consist of nucleo-protein, genes and viruses may have a similar chemical constitution.

A third group of chemical substances, trivalent arsenicals, have been found to cause a local deficiency of essential intracellular enzymes.

The tissues are conceived to carry on their activities by means of numerous chemical reactions described collectively as intermediary metabolism, and the majority of these reactions require the mediation of enzymes. These enzymes are known to consist of a protein together with a prosthetic or active group which in certain enzyme systems has been identified with a vitamin. There is evidence that genes control metabolic reactions indirectly through enzymes, and in this respect resemble hormones which are also known to play a part in the control of enzyme synthesis. Unlike genes, however, which are self-perpetuating, hormones must be synthesised.

A difference was noted in the biological manifestations produced by acid and alkaline chemical substances.

Acids are known to act as organic catalysts and so bear analogy to enzymes. On the electronic theory a substance is regarded as an acid when it can accept

a lone pair of electrons to form a covalency bond, while a base can donate a lone pair in the same way. A further analogy is seen to exist when this definition of acidity-basicity is compared with the electronic interpretation of oxidation-reduction processes, which are regarded as the acceptance or donation respectively of a lone pair of electrons without the formation of a covalency bond. The biological activity of acids is thought to be related to the protein-precipitating ability of the anion, but the activity of bases cannot be related to the nature of the cation.

Lastly, thermal burns may be caused by heated material or infra-red radiations, and are considered to be brought about by increased vibrational and rotatory movements of the atoms and molecules of the tissues, becoming manifest through protein precipitation. Similar coagulative changes are produced as the end result of severe burning by chemical agents or ionizing radiations.

Both the human eye and the eyes of laboratory animals present singularly appropriate material for studies of this kind. The tissues are easily inspected and the technical difficulties of examination have been overcome to a very large extent.

I am of the opinion that the conceptions outlined in this thesis could be extended with profitable result using the eye as the experimental medium for further investigations, and that there is a wide choice of avenues along which these studies could be pursued. The ever-

present need for a better understanding of chemical injuries of the eye may presently and at very short notice be overshadowed by the rival and more urgent claims of injuries by radiations. In the elucidation of fundamental biological processes, however, both types of activity, chemical and physical, will, of necessity, continue to have a complementary role.

"The eye, owing to its accessibility, and to the transparency and the high magnifying power of its refractive media, offers a unique opportunity for the direct observation of vital processes. It is a laboratory in which Nature is the experimenter, and into which we can look and see what is going on....." - Maitland Ramsay.

PART 4.

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Robert Leishman.

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TABLES.

TABLE 1.

SERIAL NUMBER	INITIAL	No. OF CASE RECORD	AGE IN YEARS	SEX	OCCUPATION	CAUSE OF BURNING	UNITS OF SEVERITY	DURATION OF IN-PATIENT TREATMENT IN DAYS	No. OF OUT-PATIENT ATTENDANCES	EYE AFFECTED	SKIN OF FACE	LIDS	CORNEA	CONJUNCTIVA	OTHER REGIONS	V.A. AT LAST ATTENDANCE	NOTES ON CASE
1	A.McC	36/687	17	♀	SERVANT	CLOTHES ON FIRE Thermal				L					+		SEPTIC BURNS OF TRUNK AND LIMBS METASTATIC ENDOPHTHALMITIS DIED ON 7TH DAY.
2	T.I.	36/262	43	♂	ELECTRICIAN	ELECTRIC FLASH T.	3		3	L	+	+				$\frac{6}{6}$ J1 $\frac{6}{24}$ J10	AMBLYOPIA OF L.E. SINCE CHILDHOOD
3	J.F.	36/532	18	♂	RIVETER	HOT METAL T.	1		1	L		+				$\frac{6}{5}$ J1 $\frac{6}{9}$ J1	
4	W.J.	37/95	8	♂	SCHOOL	X-RAY Radiational				L	+	+	+	+	+	— —	CANCER OF L. ANTRUM - X-RAY THERAPY DEGENERATION OF L. EYE — ENUCLEATION.
5	C.R.	37/252	28	♂	LEATHER CLOTH MANUFACTURER	CRESYLIC ACID Chemical	1		1	L		+				$\frac{6}{5}$ J1 $\frac{6}{5}$ J1	
6	J.D.	37/299	24	♂	PLUMBER	CHARCOAL T. BURN	1		1	L		+				$\frac{6}{6}$ J1 $\frac{6}{6}$ J1	
7	M.M.	37/365	36	♀	HOUSEWIFE	ANAESTHETIC C. BURN	1		1	R			+			N. R.	
8	A.A.	36/538	55	♂	MASON	LIME C.	28	22	6	R			+	+		$\frac{6}{8}$ J1 $\frac{6}{5}$ J1 c gl	RESIDUAL NEBULAR SCAR IN R. CORNEA
9	M.M.P.	37/407	8	♀	SCHOOL	CEMENT C.	24	9	15	R			+	+		$\frac{6}{36}$ $\frac{6}{6}$	RESIDUAL OEDEMA & VASCULARISATION - R CORNEA
10	E.D.	37/476	22	♂	ELECTRIC WELDER	ELECTRIC R. FLASH	1		1	B				+		$\frac{6}{9}$ $\frac{6}{9}$	
11	J.B.	37/509	35	♂	ELECTRICIAN	BOILING TAR T.	1		1	R	+		+			$\frac{6}{9}$ $\frac{6}{6}$	
12	J.B.	37/518	30	♂	ELECTRICIAN	ELECTRIC FLASH T.	1		1	L	+	+		+	+	$\frac{6}{36}$ J1 $\frac{6}{36}$ J1	MYOPIC
13	J.M.	37/541	23	♂	GALVANISER	MOLTEN METAL T.	21	16	5	B		+		+		$\frac{6}{9}$ J1 $\frac{6}{9}$ J1	
14	M.McL	37/751	34	♂	LABOURER	CHEMICAL TURPS VITRIOL C.	21	16	5	(L>R) B	+	+	R+ L+	+		$\frac{6}{5}$ J1 $\frac{6}{5}$ J1	RESIDUAL NEBULAR SCAR IN L. CORNEA
15	P.M.P.	37/641	42	♂	IRON MOULDER	MOLTEN METAL T.	2		2	L		+				$\frac{6}{6}$ J2 $\frac{6}{18}$ J12	NO EVIDENCE TO SUGGEST DEFECTIVE VISION IN L.E IS THE RESULT OF THE INJURY.
16	W.J.	37/703	21	♂		FLAME T.	2	2		B	+	+	R+ L+	+		N. R.	
17	J.A.	37/1010	26	♀	NURSEMAID	CHEMICAL C. H_2O_2			1	B						$\frac{6}{18}$ J4 J2 $\frac{6}{12}$ J4 J2	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
18	N.D.	37/1157	27	♂	LABOURER	LIME C.	2		2	L				+		$\frac{6}{4}$ J1 $\frac{6}{5}$ J1	
19	E.M.D.	37/1179	10	♂	SCHOOL	FLAME (MATCH BOX) T.	1		1	L>R B	+	+		+	NOSE	N. R.	
20	J.G.	38/135	37	♂	DRAUGHTSMAN	EXPLOSION (GAS) T.	2		2	L>R B	+	+		+		N. R.	
21	W.C.	38/1084	50	♂	ENGINEER	CEMENT C.	1		1	R				+		$\frac{6}{18}$ J12 c gl J4 $\frac{6}{18}$ J12 J6	
22	W.D	38/1217	19	♀	COOK	HOT FAT T.	2		2	B		+		+		N. R.	
23	A.B.	38/1235	19	♂	PLASTERER	LIME C.	58	28	30	R		+	+	+		$\frac{6}{60}$ $\frac{6}{6}$	OPERATION FOR SYMBLEPHARON — CONTACT GLASS RESIDUAL VASCULAR SCAR IN CORNEA.
24	T.C.	39/132	25	♂	PAINTER	CREOSOTE C.	4		4	L	+	+				$\frac{6}{5}$ $\frac{6}{12}$	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
25	J.B.	39/1070	46	♂	LABOURER	CEMENT C.	19	9	10	B			+	+		$\frac{6}{9}$ $\frac{6}{9}$	NEBULAR SCAR IN LEFT CORNEA CAUSED BY OLD INJURY.
26	W.D.	39/1781	6	♂	SCHOOL	HOT POKER T.	1		1	L	+	+				N. R.	
27	D.M.D.	40/59	34	♂	HOSTEL WARDEN	EXPLOSION OF FURNACE T.	53	49	4	R	+	+	+	+	+	c gl $\frac{6}{9}$	PERFORATING WOUND OF GLOBE - ENUCLEATION R.E.
28	H.L.	40/4	21	♂	MOTOR DRIVER	STEAM T.	2		2	L	+	+				$\frac{6}{6}$ $\frac{6}{6}$	
29	H.G.	40/687	18	♂	MEDICAL STUDENT	SULPHURIC + NITRIC ACID C.	5	3	2	B	+	+	R+ L+	+		N. R.	
30	J.C.	41/1046	41	♂	ACID MAN.	NITRIC ACID C.	5		5	R	+			+		$\frac{6}{4}$ $\frac{6}{5}$	

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31	J.McK	41/170	24	♂	GALVANISER	METAL T.	19	14	5	R	+	+		+	+	6/12 6/9	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
32	T.C	42/2	27	♂	BRICKLAYER	LIME C.			1	R						N. R.	NO OCULAR ABNORMALITY.
33	J.McC	41/309	56	♂	LABOURER	CRESYLIC ACID C.	1		1	B	+				FACE +	6/18 6/12	
34	W.F.	42/985	34	♂	CAULKER	OXYGEN T.	4	3	1	L			+	+		6/9 6/12	
35	J.M.	42/1142	34	♂	FIREMAN	FLAME T.	3		3	B	+					6/24 J1, 6/12 c̄ gl; 3/60 <J12, 6/18	HIGH MYOPIA WITH CHOROIDO-RETINAL DEGENERATION
36	P.McG	42/1352	30	♂	LABOURER	LIME C.	6	6		B			+	+		6/18 J1 6/36 J12 ATROPINE	DEFECTIVE VISION NOT FULLY ACCOUNTED FOR
37	J.C.	43/49	36	♂	PROCESS WORKER	CAUSTIC SODA C.	7	5	2	B	+	+				6/6 6/6	
38	A.C.	43/251	35	♂		HOT METAL T.	1		1	B		+	+	+		N. R.	
39	V.B.	43/1590	19	♂	STUDENT	BOILING SULPHURIC ACID M. (C+T)	1		1	L				+		N. R.	
40	D.G.	44/127	19	♂	STUDENT	Zn + HCl C.	1		1	R				+		N. R.	
41	R.C.	44/143	46	♂	MUNITION WORKER	EXPLOSION Mg Sb $KMnO_4$ T+C	48	37	11	B	+	+	+	+	+	6/6 ± gl J2 6/6	NO RESIDUAL CORNEAL LESION.
42	E.D.	44/438	20	♀	AT HOME	MASCARA C.	1		1	B	+	+				6/9 J1. 6/6 J1.	
43	R.McL	44/440	44	♂	METAL WORKER	FLAME T.	35	19	16	B	+	+	+	+	HANDS +	6/12 c̄ gl. J6 6/9 J6	NO RESIDUAL CORNEAL LESION
44	J.P.	44/605	20	♀	STUDENT	CAUSTIC SODA C.	1		1	L				+		6/5 J1 6/5 J1.	
45	R.S.	44/1247	18	♂	RIVETER	RED HOT METAL T.	11	11		L		+	+	+		6/9 J1 6/24 J12 N. R.	
46	W.V.	45/70	18	♀	STUDENT	ACETIC ACID C.	3		3	L			+	+		N. R.	
47	M.T.	45/71	19	♀	STUDENT	ACETIC ACID C.	3		3	R			+	+		N. R.	
48	R.M.	45/1123	40	♂	MOULDER	MOLTEN METAL T.	6	1	5	R		+	+	+		6/6 6/5	
49	J.B.	45/1124	17	♂	STUDENT	BOILING HNO_3 T+C	1		1	R				+		6/6 6/6	
50	J.M.	43/642	22	♂	STUDENT	HCl VAPOUR C.	6	4	2	B			+	+		6/5 6/5	
51	R.C.	43/705	20	♀	PACKER	AMMONIA SPLASH C.	12	7	5	R			+	+		6/18 6/36	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
52	M.J.	43/720	32	♀	CLEANER	LYSOL SPLASH C.	3		3	L				+		6/12 J1 6/36 J8	OLD VASCULARISED SCARS IN LEFT CORNEA CAUSE OF DEFECTIVE VISION NOT KNOWN.
53	A.Y.	43/796	27	♂	CHEMIST	HNO_3 SPLASH C.	1		1	R				+		6/6 J1 6/6 J1.	
54	J.G.	43/798	38	♂	PAINTER	NaOH SPLASH C.	2		2	R		+	+	+		6/6 J2 6/6 J2	
55	A.G.	39/279	66	♂	PLUMBER	MOLTEN LEAD T.	1		1	L				+		6/60 2/36	
56	G.C.	39/455	20	♂	BRASS MOULDER	MOLTEN BRASS T.	5		5	R	+	+	+	+		6/9 6/5	
57	K.H.	39/1417	17	♂	WIRELESS OPERATOR	BOILING H_2O T.	1		1	R				+		6/6 6/4	
58	R.McD	39/1778	23	♂	JOINER	MOLTEN LEAD T.	1		1	L	+	+				6/9 J1 6/18 J4	L.E. KNOWN TO BE AMBLYOPIC
59	L.D.	40/86	38	♂	ELECTRICITY ATTENDANT.	ELECTRIC FLASH R.	1		1	B			+	+		6/12 6/12	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
60	A.M.	40/105	24	♂	SLATER	LIME C.	1		1	R				+		6/36 6/12	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.

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61	A.E.	40/439	66	♂	RETIRED	LIME C.	3		3	L				+		$\frac{\div 9 J_1 EE}{6/18}$ $\frac{6}{18}$	CORNEAE NORMAL ON SLIT LAMP EXAMINATION TWO YEARS LATER.
62	R.M.	40/510	21	♂	STUDENT	H_2SO_4 $KMnO_4$ C.	2		2	R				+		$\frac{6}{36}$ $\frac{6}{9}$	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
63	A.M.	40/884	28	♂	SHOEMAKER	PETROL FLAME T.	1		1	B	+			+		$\frac{6}{6}$ $\frac{6}{6}$	
64	J.W.	40/1006	26	♂	ACETYLENE BURNER	BENZENE FLAME T.	1		1	B	+			+		$\frac{6}{6} J_1$ $\frac{6}{18} J_6$	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
65	D.G.	41/524	51	♂	GAS LIGHTER	GAS FLAME T.	1		1	B				+		N. R.	
66	C.F.	41/825	8	♂	SCHOOL	LIME C.	5	4	1	L			+	+		$\frac{6}{6}$ $\frac{6}{9}$	
67	J.McG	37/352	22	♂	LABOURER	CEMENT C.	1		1	R				+		$\frac{6}{12} J_4$ $\frac{6}{6} J_1$	
68	T.H.	38/587	23	♂	SCAFFOLDER	CEMENT C.	1		1	L				+		N. R.	
69	A.K.	38/1268	14	♂	LAB BOY	SULPHURIC ACID C.	1		1	R		+		+		$\frac{6}{6}$ $\frac{6}{6}$	
70	M.B	38/1359	24	♂	LAB. ASSISTANT	METHYLATED SPIRITS. C.	2		2	L				+		$\frac{6 \div 9l}{6}$ $\frac{6}{6}$	
71	J.W.	38/1190	35	♂	ENGINEER	CEMENT & SODA C.	1		1	R				+		N. R.	
72	J.McA.	40/1229	35	♂	MUNITIONS WORKER	TETRYL C.	1		1	B				+		N. R.	
73	M.G.	45/692	28	♀	HOSPITAL MAID	VIM C.	1		1	L				+		N. R.	
74	J.B.	40/113	17	♂	CARPENTER	ELECTRIC FLASH R.	1		1	B				+		N. R.	
75	R.D	41/111	22	♂	FINISHER	WELDING FLASH R.	1		1	B				+		$\frac{6}{5} J_1$ $\frac{6}{5} J_1$	
76	J.G.	40/210	25	♂	PLASTERERS LABOURER	SLAKED LIME C.	6		6	L			+	+		$\frac{6}{5}$ $\frac{6}{18}$	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
77	J.G.	40/1130	20	♂	PLASTERER'S HELPER	RED HOT STEEL T.	3	3		L		+	+			$\frac{6}{6}$ $\frac{6}{36}$	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
78	W.S.	41/125	19	♂	STUDENT	HCl. HNO_3 C. $CuSO_4$	18	14	4	L	+	+	+	+		$\frac{6}{4}$ $\frac{6}{4}$	
79	F.W.	41/234	33	♂	R.O. POLISH NAVY	BURNS AIR-RAID T.	?			L	+		+			——	TRANSFERRED FROM HOSPITAL.
80	D.R.	41/696	7	♂	SCHOOL	LIME C.	3		3	R			+	+		N. R.	
81	A.A.	41/732	40	♂	FACTORY WORKER	EXPLOSION OF POWDER C.	3	3		B			+	+		N. R.	
82	A.B.	42/965	39	♂	PICKLER	HCl. C.	8	6	2	B			+	+		$\frac{6}{9}$ $\frac{6}{18}$	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
83	R.McG	42/1218	15	♂	SLATER	LIME (SLAKED) C	6	5	1	B			+	+		$\frac{6}{4}$ $\frac{6}{4}$	
84	J.C.	45/737	58	♂	POSTAL WORKER	DISINFECTANT FLUID FOR FLOORS C.	38	38		L			+	+		$\frac{6}{6} \frac{\div 9l}{(ATROPINE)} \frac{6}{12}$	EARLY CATARACT L.E.
85	J.McP	45/774	15	♂	MESSAGE BOY	CHEMICALS IN FIRE T.	1		1	B	+		+	+	+ R.HAND	N. R.	
86	A.T.	37/706	50	♂	PLASTERER	LIME C.	1		1	L			+	+		N. R.	
87	J.S	40/211	18	♂	PLASTERER	LIME C.	1		1	L			+	+		N. R.	
88	R.N.	+2/1518	36	♂	EXPLOSIVES WORKER	TETRYL C			1	B				+		$\frac{6}{6} \frac{6}{\div 9l 6}$	MYOPIC ASTIGMATISM.
89	J.B.	45/157	17	♂	SHELLMEX WORKER	PETROL EXPLOSION T.	8	6		B	+	+	+	+		$\frac{6}{12}$ $\frac{6}{12}$	NO EVIDENCE TO ACCOUNT FOR DEFECTIVE VISION.
90	M.McK	45/1060	24	♀	FACTORY WORKER	BOILING H_2O T.	1		1	L		+		+		$\frac{6}{36} \frac{6}{\div 9l 18}$	HIGH MYOPIA

SERIAL NUMBER	INITIAL	No of CASE RECORD	AGE IN YEARS	SEX	OCCUPATION	CAUSE of BURNING.	UNITS of SEVERITY	DURATION of IN-PATIENT TREATMENT in DAYS.	No. of OUT-PATIENT ATTENDANCES.	EYE AFFECTED	SKIN of FACE	LIDS	CORNEA	CONJUNCTIVA	OTHER REGIONS	V.A. AT LAST ATTENDANCE.	NOTES ON CASE
91	N.M.S.B.	39/1508	29	♂	BRASS FINISHER	MOLTEN TAR T.	9	7	2	B	+	+	+	+		$\frac{6}{6}$ $\frac{6}{6}$	
92	A.M.W.	40/1165	49	♂	TAILOR	MUSTARD GAS C.			44	B		+	+		LEGS + CHEST	$\frac{6}{9}$ $\frac{6}{60}$ $\frac{6}{9}$ $\frac{6}{6}$	SCARS ON LEGS — BRONCHITIS
93	J.F.	45/289	35	♂	MARINE FITTER	GAS EXPLOSION T.	20	11	9	L	+	+	+	+ R WRIST →	+	$\frac{6}{6}$ $\frac{6}{6}$	RESIDUAL NEBULAR SCARS IN LEFT CORNEA
94	H.Y.	43/826	49	♂	UNEMPLOYED	MUSTARD GAS C.			6	B			++	++		$\frac{6}{18}$ J1	NIL BRONCHITIS
95	A.N.F.D.	37/521	43	♂	LABOURER	MUSTARD GAS C.			6	R			+	+		$\frac{6}{12}$ J1 $\frac{6}{6}$ J1	ARGYLL ROBERTSON PUPILS — FUNDI NORMAL.
96	J.S.	37/1141	60	♂	CHAUFFEUR	MUSTARD GAS C.			2	B				+	LENS OPACITIES	$\frac{6}{9}$ $\frac{6}{9}$	EARLY CATARACT. OPACITIES.

TABLE 2.

Year.	Total No. of Cases examined per annum.	Total No. of Cases of Recent Injury to Eye Region.
1936	646	3
1937	1404	15
1938	1513	8
1939	1821	8
1940	1538	14
1941	1216	10
1942	1624	5
1943	1647	8
1944	1525	6
1945	1300	10
Totals.	14,234	87

TABLE 3.

Years.	1936-38	1939-45	Totals.
No. of Cases of Recent Injury.	26	61	87
All other Cases.	3537	10610	14147
Totals.	3563	10671	14234
Proportional Rate % for Cases of Recent Injury.	0.73%	0.57%	

$\chi^2 = 1.097$: for n = 1, P = between 0.30 and 0.20

TABLE 4.

Age in Years.	6-10	11-15	16-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	66-70
No. of out-patient cases.	3	2	12	14	7	6	4	3	2	1	1	0	2
No. of in-patient cases.	2	1	6	4	3	5	4	1	2	1	1	0	0
Totals.	5	3	18	18	10	11	8	4	4	2	2	0	2

TABLE 5.

Age in Years.	1-20	21-40	41-70	Totals.
No. of out-patient cases.	17	31	9	57.
No. of in-patient cases.	9	16	5	30
Totals.	26	47	14	87

$\chi^2 = 0.013$: for n = 2, P = about 0.99

TABLE 6.

Age in Years.	No. of Cases.	
15 and under	8	
16-60	78	
61 and over	1	
Totals.	87.	

TABLE. 7

	No. of in-patient cases.	No. of out-patient cases.	Totals.
Males.	28	48	76
Females.	2	9	11
Totals.	30	57	87

χ^2 = 1.49: For n = 1, P = between 0.30 and 0.20

TABLE. 8

Age in Years.	Males.	Females.	Totals.
1-10	4	1	5
11-20	15	6	21
21-30	26	2	28
31-40	17	2	19
41-50	8	0	8
51-60	4	0	4
61-70	2	0	2
Totals.	76	11	87

TABLE. 9

Age in Years.	Males.	Females.	Totals.
1-20	19.	7	26
21-70	57	4	61
Totals.	76	11	87

TABLE. 10

Age in Years.	Males.	Females.	Totals.
1-20	19.5	6.5	26
21-70	56.5	4.5	61
Totals.	76	11	87

χ^2 = 5.11: For n = 1, P = between 0.05 and 0.02

TABLE. 11.

Days in Hospital.	x	1-7	8-14	15-21	22-28	29-35	36-42	43-49
No. of Patients.	y	14	7	3	2	0	2	1

TABLE. 12

No. of attendances in days.	x	1	2	3	4	5	6
No. of patients.	y	38	8	7	1	2	1

TABLE. 13

In-patient cases: without residual lesion.

Serial Number of case.	No. of Days in Hospital.	Deviations from Mean.	Squares of Deviations.
13	16	+ 6.217	38.652
16	2	- 7.783	60.575
25	9	- 0.783	0.613
29	3	- 6.783	46.009
31	14	+ 4.217	17.784
34	3	- 6.783	46.009
36	6	- 3.783	14.311
37	5	- 4.783	22.877
41	37	+27.217	740.775
43	19	+ 9.217	84.954
45	11	+ 1.217	1.482
48	1	- 8.783	77.141
50	4	- 5.783	33.443
51	7	- 2.783	7.745
66	4	- 5.783	33.443
77	3	- 6.783	46.009
78	14	+ 4.217	17.784
81	3	- 6.783	46.009
82	6	- 3.783	14.311
83	5	- 4.783	22.877
84	38	+28.217	796.209
89	8	- 1.783	3.180
91	7	- 2.783	7.745
Totals. 23	225		2179.937
Mean.	9.783		

In-patient cases; with residual lesion.

8	22	- 0.5	0.25
9	9	-13.5	182.25
14	16	- 6.5	42.25
23	28	+ 5.5	30.25
27	49	+26.5	702.25
93	11	-11.5	132.25
Totals. 6	135		1089.50
Mean.	22.5		

t = 2.511: For n = 27, P = between 0.02 and 0.01

TABLE 14.

Severity values based on No. of days of in-patient treatment.	No. of cases with residual lesion.	No. of cases without residual lesion.	Totals.
20 and under.	3 (a)	21 (b)	24 (a+b)
21 and over.	3 (c)	2 (d)	5 (c+d)
Totals.	6 (a+c)	23 (b+d)	29 (n)

Exact Method: P = 0.046

χ^2 (with Yates' Correction)= 3.163:for n = 1, P = about 0.076

TABLE 15.

Units of Severity (in-patient cases)	No. of cases with residual lesion.	No. of cases without residual lesion.	Totals.
20 and under.	1	19	20
21 and over.	5	4	9
Totals.	6	23	29

Exact Method: P = 0.00548

χ^2 (with Yates' Correction) = 6.540: for n = 1, P = 0.0105

TABLE 16.

Units of Severity (all cases).	No. of cases with residual lesion.	No. of cases without residual lesion.	Totals.
20 and under.	1	76	77
21 and over.	5	4	9
Totals.	6	80	86

Exact Method: P = 0.00002

TABLE. 17

No. of cases with Eye intact.	No. of cases with Eye involved.					
Face and lids affected.	Right Eye		Left Eye		Both Eyes.	
	Conjunctiva only	Cornea also	Conjunctiva only	Cornea also	Conjunctiva only	Cornea also
	12	12	11	12	11	16
13	24		23		27	
13			74			

TABLE. 18

Chemical.			Thermal.			Combined Chemical and Thermal.	Radiational.
Acids.	Alkalis.	Miscellaneous.	Solids.	Liquids.	Vapours.		
13	22	10	7	11	17		
45			35			3	4

TABLE 19

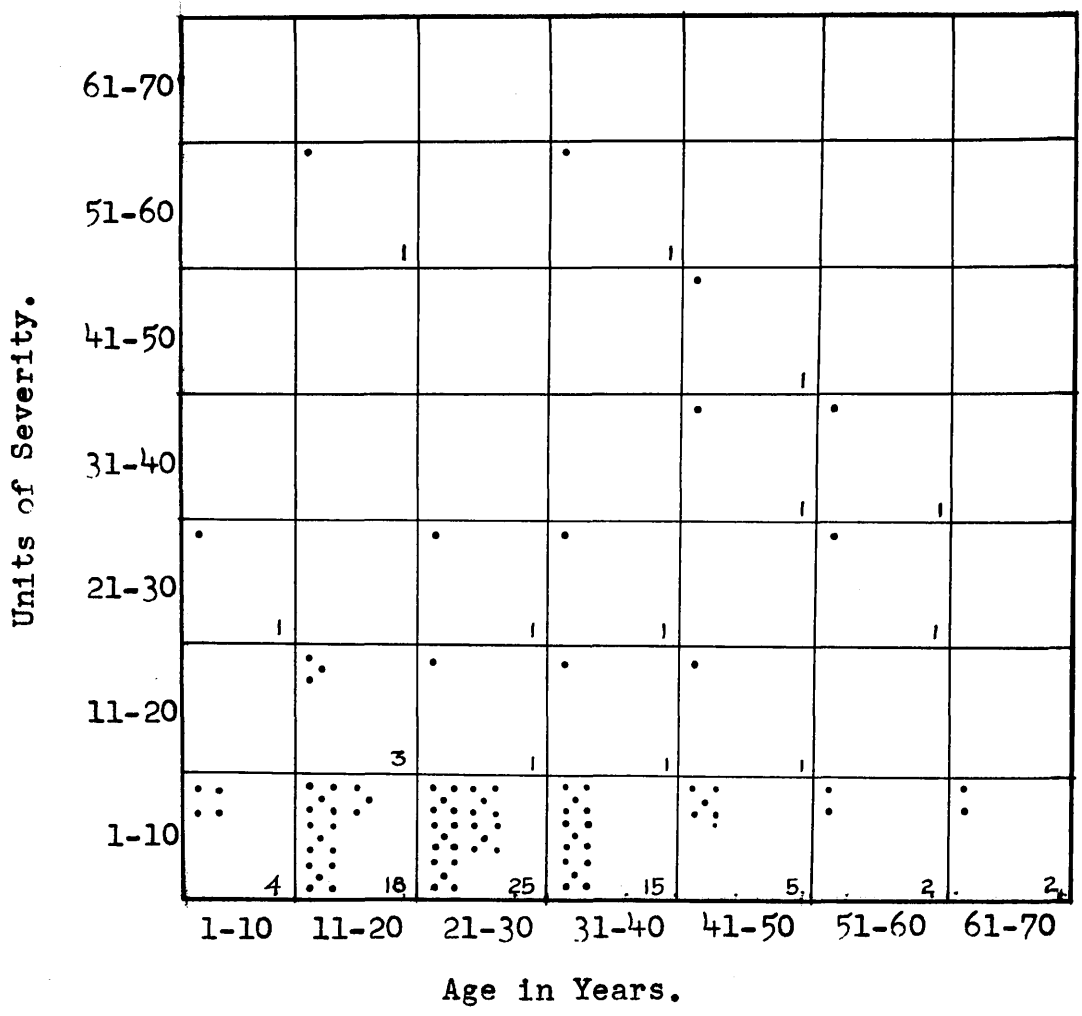
61-70
51-60
41-50
31-40
21-30
11-20
1-10
Units of Severity.
4
18
25
15
5
2
2
1
1
1
1
1
1
1
1
1
1
1
1
3
1
1
1
1-10
11-20
21-30
31-40
41-50
51-60
61-70
Age in Years.

TABLE. 20

Age in Years.	Right Eye	Left Eye	Both Eyes.
1-10	2	1	1
11-20	8	7	6
21-30	5	7	6 (3)
31-40	6	4	6 (1)
41-50	2	1	3
51-60	1	1	1
61-70	0	2	0
Totals.	24	23	23 (27)

TABLE. 21

Age in Years.	Right Eye.	Left Eye	Totals.
20 and under	10	8	18
21 and over	14	15	29
Totals.	24	23	47

$\chi^2 = 0.235$: For n = 1, P = about 0.66

TABLE 22.

Age in Years.	Face and Lids affected.	Conjunctiva only.	Cornea also
1-10	1	1	3
11-20	2	8	13
21-30	5	16	5
31-40	2	4	13
41-50	2	2	4
51-60	1	1	2
61-70	0	2	0
Totals.	13	34	40

TABLE 23 (A).

Age in Years.	Face and Lids affected.	Conjunctiva only.	Totals.
20 and under.	3	9	12
21 and over.	10	25	35
Totals.	13	34	47

$\chi^2 = 0.018$: For n = 1, P = about 0.9

TABLE 23 (B).

Age in Years.	Conjunctiva only.	Cornea also.	Totals.
20 and under.	9	16	25
21 and over.	25	24	49
Totals.	34	40	74

$\chi^2 = 1.506$: For n = 1, P = about 0.23

TABLE. 24

Age in Years.	Chemical.	Thermal.	Combined. Chemical and Thermal.	Radiational
1-10	3	2	0	0
11-20	12	7	2	1
21-30	13	12	0	2
31-40	10	9	0	1
41-50	3	3	1	0
51-60	3	1	0	0
61-70	1	1	0	0
Totals.	45	35	3	4

TABLE. 25

Age in Years.	Chemical	Thermal	Totals.
20 and under	15	9	24
21 and over	30	26	56
Totals.	45	35	80

$\chi^2 = 0.544$: For n = 1, P = about 0.48

TABLE. 26

Age in Years.	Defective Vision before accident.	Defective Vision due to accident.	Defective Vision cause unknown.	Adequate Vision after accident.
1-10	0	1	0	1
11-20	1	1	2	9
21-30	5	0	4	15
31-40	2	1	2	7
41-50	2	0	2	3
51-60	1	0	0	2
61-70	2	0	0	0
Totals.	13	3	10	37

TABLE. 27

Age in Years.	Cases with Defective Vision.	Cases with Adequate Vision.	Totals.
30 and under	14	25	39
31 and over	12	12	24
Totals.	26	37	63

χ^2 = 1.218: For n = 1, P = about 0.27

TABLE 28.

Units of Severity.	Males.	Females.	Totals.
20 and under.	67	10	77
21 and over.	8	1	9
Totals.	75	11	86

Exact Method : P = 0.406

TABLE 29.

Sex.	Right Eye.	Left Eye.	Both Eyes.	Totals.
Females.	5	4	1	10
Males.	18	20	22	60
Totals.	23	24	23	70

TABLE 30 (A)

Sex.	Right Eye.	Left Eye.	Totals.
Females.	5	4	9
Males.	18	20	38
Totals.	23	24	47

TABLE 30 (B)

Sex.	Right Eye.	Left Eye.	Totals.
Females.	4.5	4.5	9
Males.	18.5	19.5	38
Totals.	23	24	47

χ^2(with Yates' Correction)= 0.05
for n = 1, P = about 0.82

TABLE 31 (A)

Sex.	Right Eye.	Both Eyes.	Totals.
Females.	5	1	6
Males.	18	22	40
Totals.	23	23	46

TABLE 31 (B)

Sex.	Right Eye.	Both Eyes.	Totals.
Females.	4.5	1.5	6
Males.	18.5	21.5	40
Totals.	23	23	46

χ^2(with Yates' Correction)= 1.73
for n = 1, P = about 0.19

TABLE 32.

Sex.	Face and Lids affected.	Conjunctiva only.	Cornea also.	Totals.
Females.	1	5	5	11
Males.	12	29	35	76
Totals.	13	34	40	87

TABLE 33 (A)

Sex.	Face and Lids affected.	Conjunctiva only.	Totals.
Females.	1	5	6
Males.	12	29	41
Totals.	13	34	47

TABLE 33 (B).

Sex.	Face and Lids affected.	Conjunctiva only.	Totals.
Females.	1.5	4.5	6
Males.	11.5	29.5	41
Totals.	13	34	47

χ^2 (with Yates' Correction) = 0.024
For n = 1, P = about 0.88

TABLE 34.

Sex.	Conjunctiva only.	Cornea also.	Totals.
Females.	5	5	10
Males.	29	35	64
Totals.	34	40	74

χ^2 = 0.076: For n = 1, P = about 0.78

TABLE 35.

Sex.	Chemical.	Thermal.	Combined Chemical & Thermal.	Radiational.
Females.	9	2	0	0
Males.	36	33	3	4
Totals.	45	35	3	4

TABLE 36 (A).

Sex.	Chemical.	Thermal.	Totals.
Females.	9	2	11
Males.	36	33	69
Totals.	45	35	80

TABLE 36 (B).

Sex.	Chemical.	Thermal.	Totals.
Females.	8.5	2.5	11
Males.	36.5	32.5	69
Totals.	45	35	80

χ^2 (with Yates' Correction) = 2.228: For n = 1, P = 0.13

TABLE 37.

Sex.	Defective Vision before accident.	Defective Vision due to accident.	Defective Vision cause unknown.	Adequate Vision after accident.
Females.	3	1	0	2
Males.	10	2	10	35
Totals.	13	3	10	37

TABLE 38 (A).

Sex.	Cases with Defective Vision.	Cases with Adequate Vision.	Totals.
Females.	4	2	6
Males.	22	35	57
Totals.	26	37	63

TABLE 38 (B).

Sex.	Cases with Defective Vision.	Cases with Adequate Vision.	Totals.
Females.	3.5	2.5	6
Males.	22.5	34.5	57
Totals.	26	37	63

χ^2 (with Yates'Correction)= 0.797: for n = 1,P = about 0.37

TABLE 39 (A).

Units of Severity.	Right Eye.	Left Eye.	Both Eyes.
1-10	18	18	22
11-20	2	3	1
21-30	2	0	2
31-40	0	1	1
41-50	0	0	1
51-60	2	0	0
Totals.	24	22	27

TABLE 39 (B).

Units of Severity.	Right Eye.	Left Eye.	Both Eyes.
10 and under	18	18	22
11 and over	6	4	5
Totals.	24	22	27

TABLE 40.

Units of Severity.	Right Eye.	Left Eye.	Totals.
10 and under	18	18	36
11 and over	6	4	10
Totals.	24	22	46

Exact Method: P = 0.258

TABLE 41.

Units of Severity.	Unilateral lesion.	Bilateral lesion.	Totals.
10 and under	36	22	58
11 and over	10	5	15
Totals.	46	27	73

Exact Method: P = 0.240

TABLE. 42.

Units of Severity.	Face and Lids affected.	Conjunctiva only.	Cornea also.
1-5	12	32	18
6-10	1	0	8
11-15	0	0	2
16-20	0	1	3
21-25	0	1	2
26-30	0	0	1
31-35	0	0	1
36-40	0	0	1
41-45	0	0	0
46-50	0	0	1
51-55	0	0	1
56-60	0	0	1
Totals.	13	34	39

TABLE 43.

Units of Severity.	Face and Lids affected.	Conjunctiva only.	Totals.
5 and under	12	32	44
6 and over	1	2	3
Totals.	13	34	47

Exact Method: P = 0.453

TABLE 44.

Units of Severity.	Face, Lids and Conjunctiva affected.	Cornea also.	Totals.
5 and under	44	18	62
6 and over	3	21	24
Totals.	47	39	86

Exact Method: P = about 0.0000008.

TABLE. 45

Units of Severity.	Chemical. Acids.	Alkalis.	Miscellaneous.	Thermal. Solids.	Liquids.	Vapours.	Combined. Chemical & Thermal.	Radiational
1-5	10	13	8	5	8	12	2	4
6-10	2	4	0	0	2	1	0	0
11-15	0	1	0	1	0	0	0	0
16-20	1	1	0	1	0	1	0	0
21-25	0	1	1	0	1	0	0	0
26-30	0	1	0	0	0	0	0	0
31-35	0	0	0	0	0	1	0	0
36-40	0	0	1	0	0	0	0	0
41-45	0	0	0	0	0	0	0	0
46-50	0	0	0	0	0	0	1	0
51-55	0	0	0	0	0	1	0	0
56-60	0	1	0	0	0	0	0	0
Totals.	13	22	10	7	11	16	3	4

TABLE. 46

Units of Severity.	Chemical.	Thermal.	Totals.
5 and under	31	25	56
6 and over	14	9	23
Totals.	45	34	79

Exact Method: P = about 0.200

TABLE. 47(A)

Units of Severity.	Acids.	Miscellaneous Chemicals.	Totals.
5 and under	10	8	18
6 and over	3	2	5
Totals.	13	10	23

Exact Method: P = 0.4095

TABLE. 47 (B)

Units of Severity.	Acids.	Alkalis.	Totals.
5 and under	10	13	23
6 and over	3	9	12
Totals.	13	22	35

Exact Method P * 0.2031

TABLE. 48 (A)

Units of Severity.	Solids.	Liquids.	Totals.
5 and under	5	8	13
6 and over	2	3	5
Totals.	7	11	18

Exact Method P = 0.4506

TABLE. 48 (B)

Units of Severity.	Liquids.	Vapours.	Totals.
5 and under	8	12	20
6 and over	3	4	7
Totals.	11	16	27

Exact Method P = 0.3744

TABLE. 49

Units of Severity.	Defective Vision before accident.	Adequate Vision before accident.
1-5	11	23
6-10	1	5
11-15	1	0
16-20	0	4
21-25	0	2
26-30	0	1
31-35	0	0
36-40	0	1
41-45	0	0
46-50	0	1
51-55	0	0
56-60	0	0
Totals.	13	37

TABLE. 50

Units of Severity.	Defective Vision before accident.	Adequate Vision before accident.	Totals.
5 and under	11	23	34
6 and over	2	14	16
Totals.	13	37	50

Exact Method; P = about 0.105

TABLE 51.

Nature of Agency.	Right Eye.	Left Eye.	Both Eyes.
Chemical.	17	14	9
Thermal.	6	8	13
Combined Chemical & Thermal.	1	1	1
Radiational.	0	0	4
Totals.	24	23	27

TABLE 52.

Nature of Agency.	Right Eye.	Left Eye.	Totals.
Chemical.	17(a)	14(b)	31(a+b)
Thermal.	6(c)	8(d)	14(c+d)
Totals.	23	22	45

χ^2(with Yates' Correction)= 0.178:for n = 1, P = about 0.74

TABLE 53.

Nature of Agency.	Unilateral lesion.	Bilateral lesion.	Totals.
Chemical.	31	9	40
Thermal.	14	13	27
Totals.	45	22	67

χ^2 = 4.808: for n = 1, P = 0.028

TABLE 54.

Nature of Agency.		Unilateral lesion.	Bilateral lesion.
Chemical.	Acids.	8	3
	Alkalis.	18	3
	Miscellaneous.	5	3
Thermal.	Solids.	4	1
	Liquids.	5	3
	Vapours.	5	9

TABLE. 55

Physical State.	Unilateral lesion.	Bilateral lesion.
Solids.	4	1
Liquids.	36	12
Vapours.	5	9
Totals.	45	22

TABLE. 56

Physical State.	Unilateral lesion.	Bilateral lesion.	Totals.
Solids.	4	1	5
Liquids.	36	12	48
Totals.	40	13	53

Exact Method: P = 0.4174

TABLE. 57

Physical State.	Unilateral lesion	Bilateral lesion.	Totals.
Solids and Liquids.	40	13	53
Vapours.	5	9	14
Totals.	45	22	67

Exact Method: P = 0.013

TABLE. 58

Nature of Agency.	Face and Lids affected.	Conjunctiva only.	Cornea also.
Chemical.	5	17	23
Thermal.	8	12	15
Combined Chemical & Thermal.	0	2	1
Radiational.	0	3	1
Totals.	13	34	40

TABLE. 59(A)

Nature of Agency.	Face and Lids affected.	Conjunctiva only.	Totals.
Chemical.	5	17	22
Thermal.	8	12	20
Totals.	13	29	42

Exact Method: P = about 0.38

TABLE. 59(B)

Nature of Agency.	Face, Lids and Conjunctiva affected.	Cornea also.	Totals.
Chemical.	22	23	45
Thermal.	20	15	35
Totals.	42	38	80

Exact Method: P = about 0.50

TABLE 60.

Visual Acuity.	Right Sided Lesion.	Left Sided Lesion.	Bilateral Lesion.
Defective Vision before accident.	3	7	3
Adequate Vision before accident.	13	12	12

TABLE 61.

Visual Acuity.	Unilateral Lesion.	Bilateral Lesion.	Totals.
Defective Vision before accident.	10	3	13
Adequate Vision before accident.	25	12	37
Totals.	35	15	50

χ^2 (with Yates' Correction) = 0.079
For n = 1, P = about 0.78

TABLE 62.

Visual Acuity.	Face and Lids affected.	Conjunctiva only.	Cornea also.
Defective Vision before accident.	4	7	2
Adequate Vision before accident.	7	14	16
Totals.	11	21	18

TABLE 63.

Visual Acuity.	Face and Lids affected.	Conjunctiva only.	Totals.
Defective Vision before accident.	4	7	11
Adequate Vision before accident.	7	14	21
Totals.	11	21	32

χ^2 (with Yates' Correction) = 0.049
For n = 1, P = about 0.86

TABLE 64

Visual Acuity.	Face, Lids and Conjunctiva affected.	Cornea only.	Totals.
Defective Vision before accident.	11	2	13
Adequate Vision before accident.	21	16	37
Totals.	32	18	50

χ^2(with Yates' Correction)= 2.144. For n = 1, P = about 0.15

TABLE 65 (A).

Nature of Agency.	Defective Vision before accident.	Adequate Vision before accident.
Chemical.	6	13
Thermal.	7	21
Combined Chemical & Thermal.	0	1
Radiational.	0	2
Totals.	13	37

TABLE 65 (B).

Nature of Agency.	Defective Vision before accident.	Adequate Vision before accident.	Totals.
Chemical.	6	13	19
Thermal.	7	21	28
Totals.	13	34	47

χ^2 = 0.026: for n = 1, P = about 0.87

TABLE 66.

No.	Name.	Age.	Group.	Conjunctiva.	Cornea.	Staining.	Day of Exam.	Notes.
1.	G.S.	19	II	+ R & L	EB	-	5,6,& 9	Hydropic cells.
2.	T.C.	34	II	-	EB	-	5,6,& 9	Hydropic cells.
3.	W.B.	19	II	++ R & L	EB slight	-	5,6,& 9	Oedema lids Sub.conj. haems.
4.	J.B.	19	I	+ R & L	clear	-	5,6,& 9	Normal 9th day.
5.	J.R.	25	III	+++ R & L	EB++ R & L	+LE	5,6,9, 25,34, 40,47 54,63, & 88.	Erythema of face. Blisters of arm.
6.	F.B.	19	II	++ R & L	EB R & L	+LE	5,6,9, 25,34, 40,47, 54,63, & 88.	Erythema of face.
7.	W.M.	23	II	slight	EB in 'band'	-	5,6,& 9	Hudson's line RE.
8.	G.L.	29	II	++ R & L	EB in 'band'	-	5,6,& 9	-
x 9.	L.G.	40	II	slight	EB R & L	-	5,6,& 9	Sticky lids. Blisters of arm and scrotum.
10.	G.D.	32	I	slight	clear	-	5.6.& 9	Oedema of lids.
11.	J.S.	21	III	+++ pallor	EB++	-	5,6,9, 25,34, 40,47, 54,63, & 88.	Oedema of lids. Discharge. Sub-conj. haems.
12.	J.K.	37	I	-	clear	-	5,6,& 9	-
13.	H.B.	21	II	+ faint	EB	-	6.	Erythema of lids.
14.	E.B.	33	I	-	clear	-	6.	-

TABLE 66 (continued)

No.	Name.	Age.	Group.	Conjunctiva.	Cornea.	Staining.	Day of exam.	Notes.
15.	W.L.	37	I	slight	clear	-	6.	-
16.	C.M.	41	II	-	EB LE faint.	-	6.	Watery discharge. Sore throat.
17.	H.H.	22	I	-	clear	-	6.	-
18.	E.B.	21	I	slight	clear	-	6.	Erythema of face.
19.	A.M.	30	I	-	clear	-	6.	Photophobia was marked.
20.	H.C.	20	I	-	clear	-	6.	-
21.	F.H.	26	I	-	clear	-	6.	Erythema of face.
22.	C.B.	38	I	-	clear	-	6.	-
23.	F.C.	24	I	slight R & L	clear	-	6.	Erythema of face.
24.	J.R.	38	I	-	clear	-	6.	Lids had been swollen.
25.	J.T.	20	I	-	clear	-	6.	Sore throat.

EB = epithelial bedewing.

x This man painted the grates.

Numbers 5,6 & 11 slept in the same room; their heads were about 2 - 3 ft. from the grate.

Several men amongst numbers 1 - 12 had developed sore throats when seen on the 9th. day.

All were discharged by the 28th. day except number 5, 6 & 11. Number 11 appeared to be the worst case on the 28th. day.

TABLE 67.

Test Substances arranged by Chemical Constitution.

	COMPOUND.	ACTIVITY.
	ARSENICALS.	
1.	βchlorovinyl dichlorarsine.	XXXX
2.	Phenyl dichlorarsine.	XXXX
3.	Methyl dichlorarsine.	XXX
4.	Ethyl dichlorarsine.	XX
5.	Diphenyl cyanoarsine.	XX
6.	Diphenyl chloroarsine.	XXX
7.	ββdichlor diethyl methyl arsine.	XXX(X)
8.	ββdichlor diethyl ethyl arsine.	XXX(X)
9.	βchloroethyl dimethyl arsine.	XXX(X)
10.	βchloroethyl diethyl arsine.	XXX(X)
	NITROSAMINES.	
11.	N carbomethoxy βchloroethyl nitrosamine.	XXXX
12.	N carbomethoxy β(β chloroethylβthio) ethyl nitrosamine..	XXXX
13.	N carbomethoxyβbromoethyl nitrosamine.	XXX
14.	N carbomethoxy methyl nitrosamine..	X
15.	βchloroethyl methyl nitrosamine.	0(X)
16.	N carbomethoxyβchloroethylamine.	0(X)
17.	ββdichlor diethyl nitrosamine.	0(X)
	NITROGEN MUSTARD ANALOGUES.	
18.	ββdichlor diethyl methylamine.	XXXX
19.	ββdichlor diethyl sulphide plus ββdichlor diethyl methylamine (40:60).	XXXX
20.	ββdichlor diethyl ethylamine.	XXX
21.	ββdichlor diethyl n-propylamine.	X
22.	ββdichlor diethyl allylamine.	0(X)
23.	βchloroethyl βchloropropyl methylamine.	XX
24.	ββchloro di n-propyl methylamine.	0(X)
25.	βchloroethyl γchloropropyl methylamine.	X
26.	N ββdichlor diethyl O-methyl hydroxylamine.	0(X)
27.	Trichlor triethylamine.	XXX
28.	ββchloroethyl cyanamide.	0(X)
29.	N chloro di(βchloroethyl)amine.	X
30.	N βchloroethyl morpholine.	0(X)
31.	βchloroethyl dimethylamine.	X
	MUSTARD ANALOGUES.	
32.	ββdichlor diethyl sulphide.	XXX
33.	ββdichlor diethyl sulphide plus dimethyl sulphide (60:40).	XXX

TABLE 67 (continued)

COMPOUND.	ACTIVITY.
34. ββdichlor diethyl sulphide plus dimethyl sulphide (50:50).	XXX
35. 22 di(βchloroethyl thio) diethyl ether.	XX
36. ββdichlor diethyl sulphide plus 22 di (βchloro-ethyl thio)diethyl ether (60:40).	XXX
37. ββdichlor diethyl sulphone.	0(X)
38. βchloroethylβchlorovinyl sulphide.	XX
39. βchloroethylβchloroisopropyl sulphide.	XX
40. Methyl βchloroethyl sulphide.	XX
41. ββdichlor diethyl sulphide plus methylβchloro-ethyl sulphide (60:40).	XX
42. βethoxyethyl βchloroethyl sulphide.	X
OTHER SUBSTANCES.	
43. Methyl chloroformate.	0
44. Diethyl fluorophosphonate.	0
45. Di-isopropyl fluorophosphonate.	0

TABLE 68.

Compounds shown in Table 67 arranged by activity and approximate order of severity of action in the eye.

ACTIVITY.	RESPONSE OF ARSENICAL TYPE.	RESPONSE OF NITROSAMINE TYPE.	RESPONSE OF NITROGEN MUSTARD TYPE.	RESPONSE OF MUSTARD TYPE.	UNCLASSIFIED ON ACCOUNT OF LOW ACTIVITY.
VERY SEVERE (XXXX)	1 2 7 & 8	11 12	18 19		
SEVERE (XXX)	9 & 10 3 6	13	20	32,36,34, 33 & 27	
MODERATE (XX)	4 5			23,38 & 39 35 40 & 41	
SLIGHT (X)					29,21,42, 25,31,14, 26,22,15, 24,16,28, 30,37 & 17.
NIL(0)					43,44 & 45.

In this table the compounds are represented by the serial numbers given in Table 67.

TABLE 69.

Classification of Injury.	Group.	Clinical Features.	Treatment.
Chemical Ophthalmia.	1.	Very Mild. Lids:- red, sometimes oedema. Conjunctiva:- congested sometimes discharge. Cornea:- clear.	Bland treatment.
	11.	Mild. (additional features) Lids:- blepharospasm. Conjunctiva:- thrombosis and haemorrhages. Cornea:- epithelial desquamation and Oedema.	Bland treatment and Mydriatics.
Chemical Keratitis. (and Iritis).	111.	Severe.(additional features) Cornea:- oedema of the substantia propria.	Bland treatment. Mydriatics. Hospital.
	1V.	Very Severe. (additional features) Cornea:- prolonged keratitis, sometimes degenerative changes. Iris:- sometimes iritis.	Long term treatment.

PHOTOGRAPHS.

THE ANTERIOR LAYERS OF THE CORNEA.

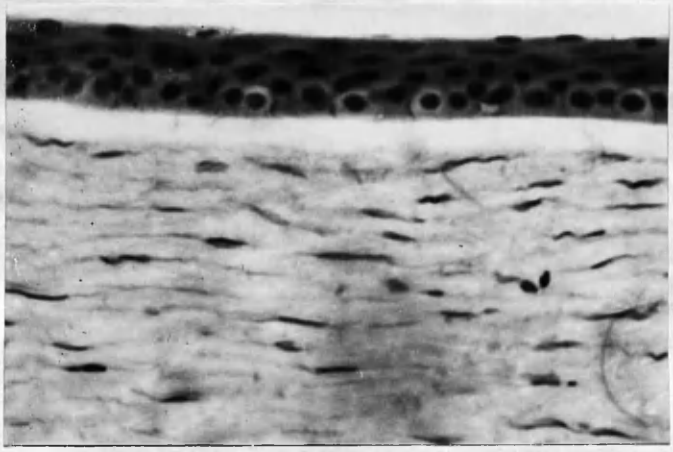

Fig. 1. MAN.

The epithelium is about 6 cell layers thick and Bowman's membrane is well developed.

THE ANTERIOR LAYERS OF THE CORNEA.

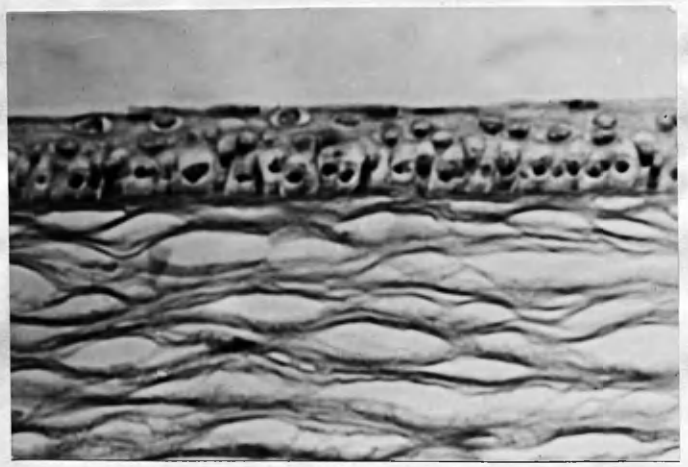

Fig. 2. RABBIT.

The epithelium is about 4 cell layers thick and Bowman's membrane is absent.

THE ANTERIOR LAYERS OF THE CORNEA.

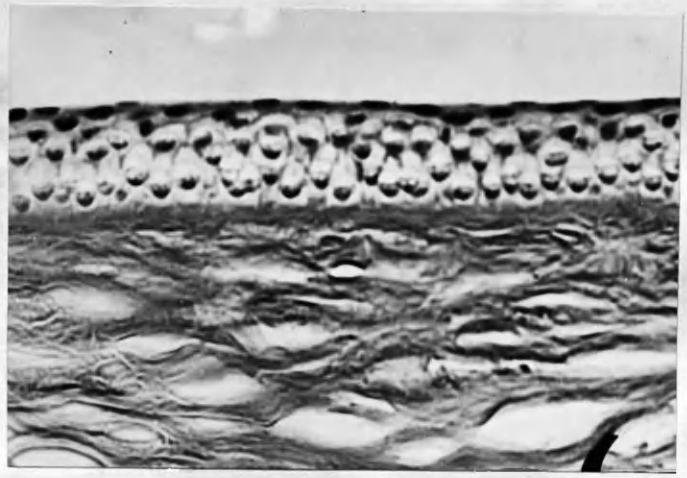

Fig. 3. MONKEY.

The epithelium is about 6 cell layers thick and Bowman's membrane is poorly defined but is present.

THE ANTERIOR LAYERS OF THE CORNEA.

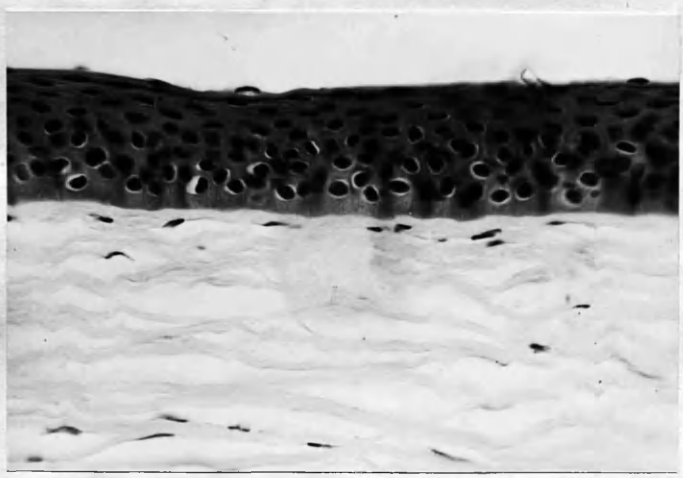

Fig. 4. DOG.

The epithelium is about 10 cell layers thick and Bowman's membrane is absent.

THE ANTERIOR LAYERS OF THE CORNEA.

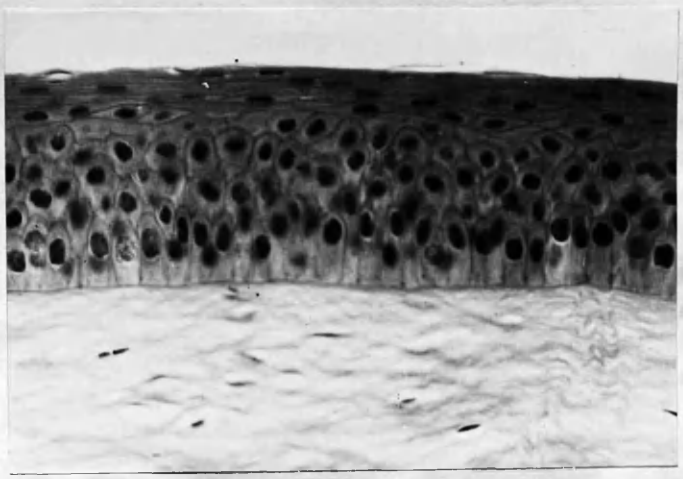

Fig. 5. GOAT.

The epithelium is about 10 cell layers thick and Bowman's membrane is absent.

THE ANTERIOR LAYERS OF THE CORNEA.

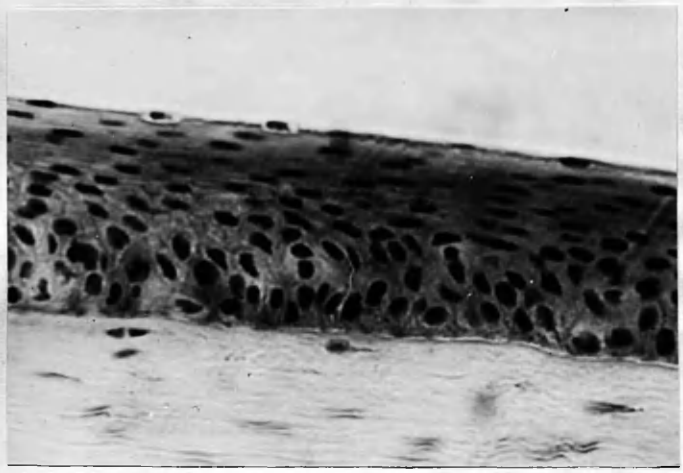

Fig. 6. HORSE.

The epithelium is about 15 cell layers thick in this specimen, and Bowman's membrane is absent.

THE POSTERIOR LAYERS OF THE CORNEA.

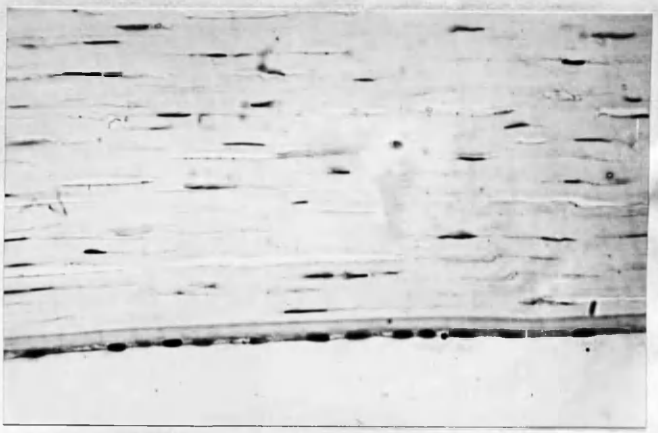

Fig. 7. MAN.

Descemet's membrane is well defined.

THE POSTERIOR LAYERS OF THE CORNEA.

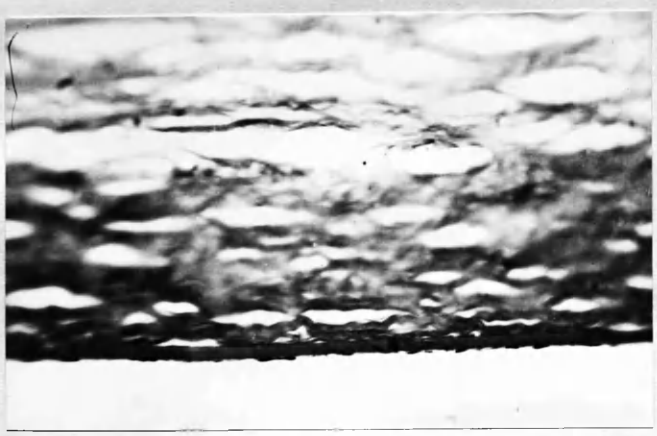

Fig. 8. RABBIT.

Descemet's membrane is present.

THE POSTERIOR LAYERS OF THE CORNEA.

Fig. 9. MONKEY.

Descemet's membrane is present but is poorly defined.

THE POSTERIOR LAYERS OF THE CORNEA.

Fig. 10. DOG.

Descemet's membrane is well defined.

THE POSTERIOR LAYERS OF THE CORNEA.

Fig. 11. GOAT.

Descemet's membrane is well defined.

THE POSTERIOR LAYERS OF THE CORNEA.

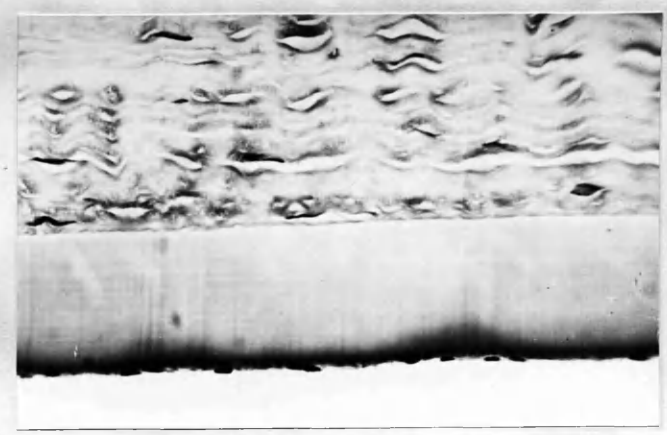

Fig. 12. HORSE.

Descemet's membrane is exceptionally well developed

PIGMENTATION AT THE LIMBUS.

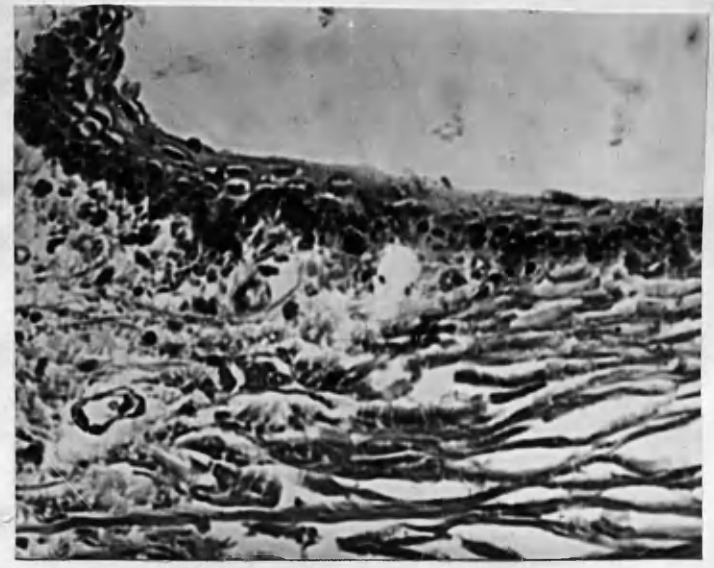

Fig. 13. RABBIT.

Melanin pigment is present in the deep layers of the epithelium at the limbus.

A FLOCCULE IN THE IRIS.

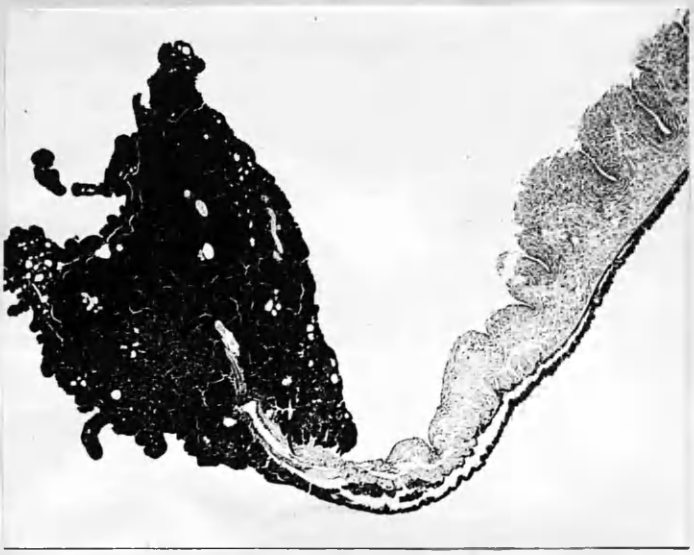

Fig. 14. HORSE.

The floccule is seen as a mass of pigmented cells with a core of iris stroma.

THE ANGLE OF THE ANTERIOR CHAMBER.

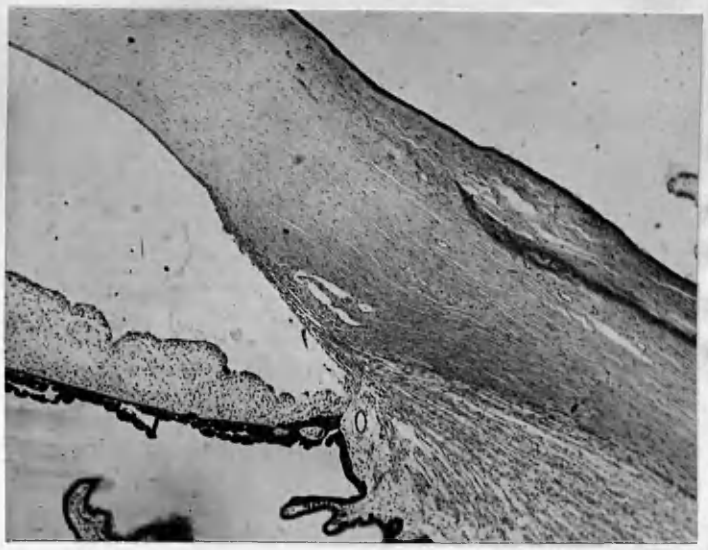

Fig. 15. MAN.

There is an absence of scleral pigmentation. The ciliary body is well developed and the major arterial circle is seen in its anterior part.

THE ANGLE OF THE ANTERIOR CHAMBER.

Fig. 16. MONKEY.

There is an absence of scleral pigmentation. A well developed, muscular, ciliary body is present.

THE ANGLE OF THE ANTERIOR CHAMBER.

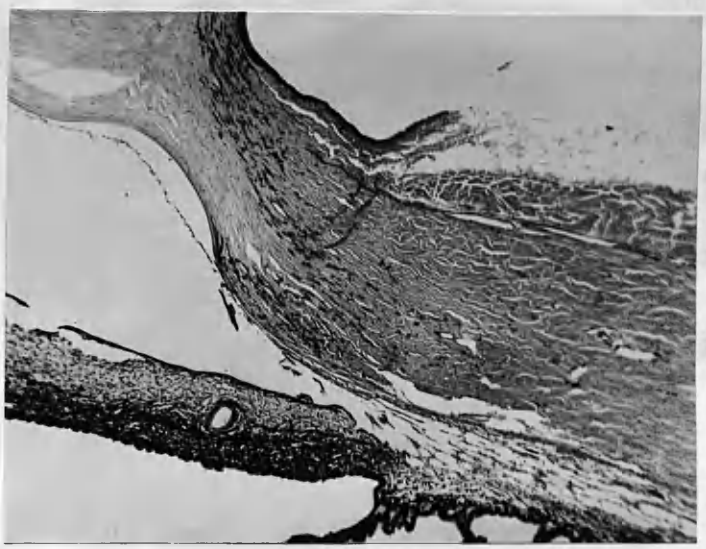

Fig. 17. DOG.

There is pigmentation of the sclera at the sclero-corneal junction. The ciliary body is poorly developed.

THE ANGLE OF THE ANTERIOR CHAMBER.

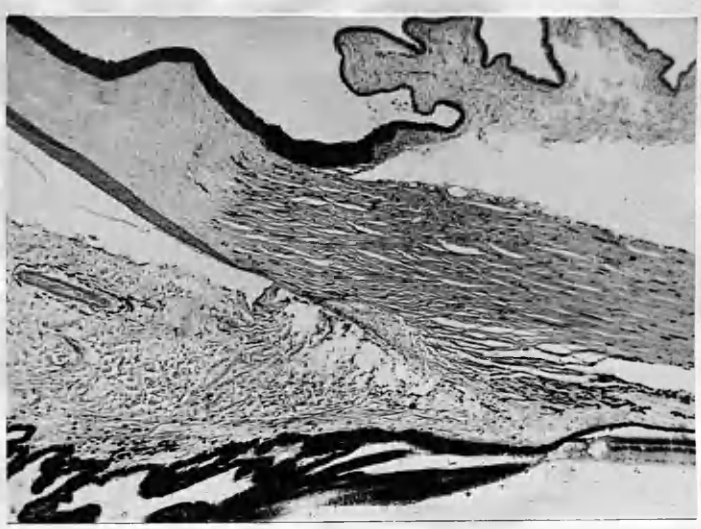

Fig. 18. GOAT.

There is pigmentation of the sclera beyond the sclero-corneal junction. The ciliary body is poorly developed.

THE ANGLE OF THE ANTERIOR CHAMBER.

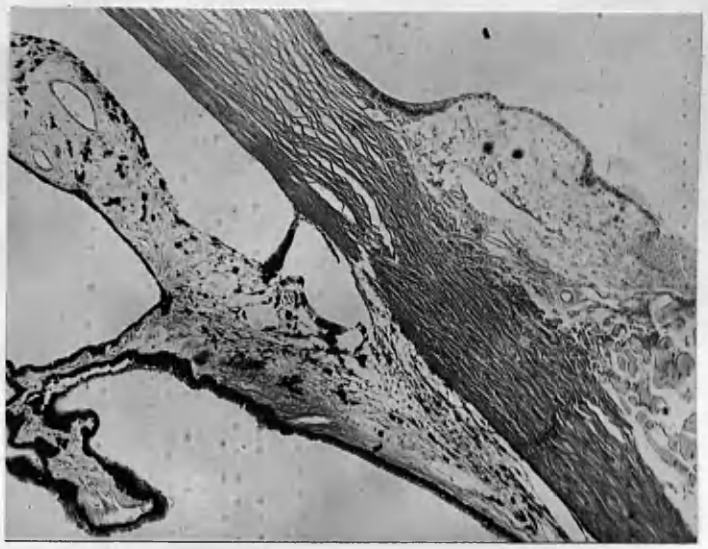

Fig. 19. RABBIT.

There is an absence of scleral pigmentation. The iris is attached to Descemet's membrane across the angle. The ciliary body is poorly developed.

THE ANGLE OF THE ANTERIOR CHAMBER.

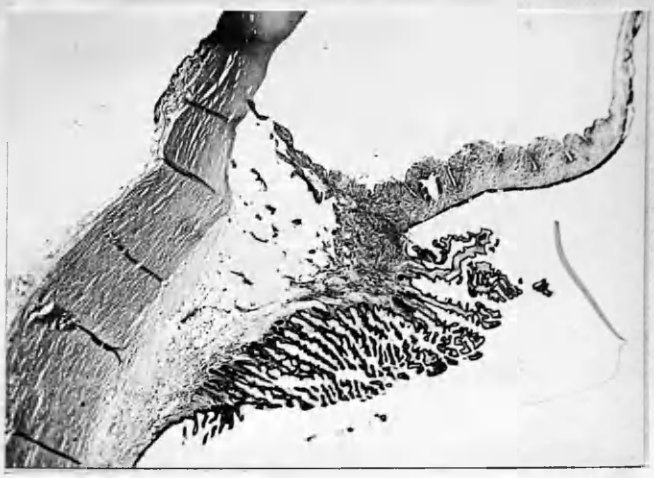

Fig. 20. HORSE.

There is an absence of scleral pigmentation. The iris is attached to Descemet's membrane across the angle. The ciliary body is poorly developed.

THE CILIARY PROCESSES.

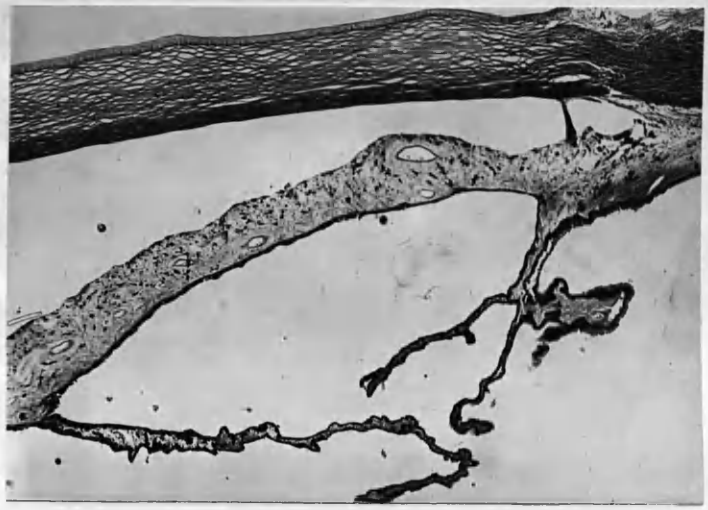

Fig. 21. RABBIT.

The major arterial circle lies near the root of the iris. The ciliary processes are of simple pattern and arise from both the iris and the ciliary body.

THE CILIARY PROCESSES.

Fig. 22. HORSE.

The ciliary processes are of complex pattern.

THE IRIS.

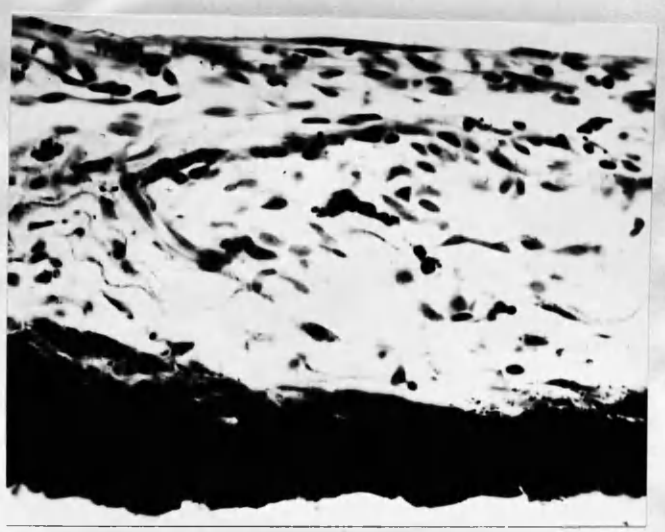

Fig. 23. MAN.

The stroma is of delicate texture and chromatophores are relatively scanty.

THE IRIS.

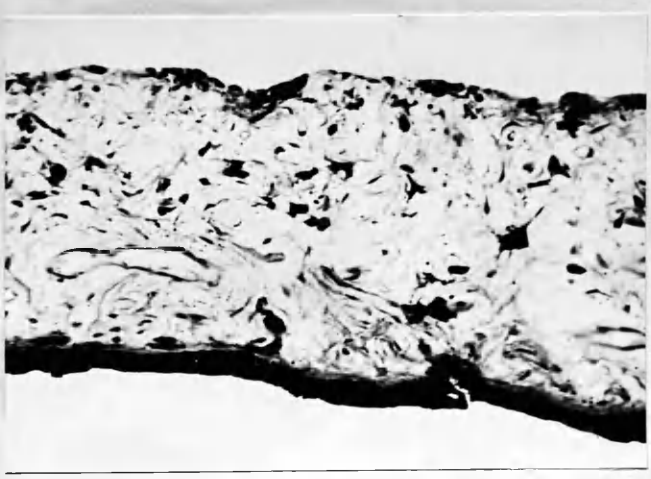

Fig. 24. RABBIT.

The stroma is of delicate texture and chromatophores are relatively scanty.

THE IRIS.

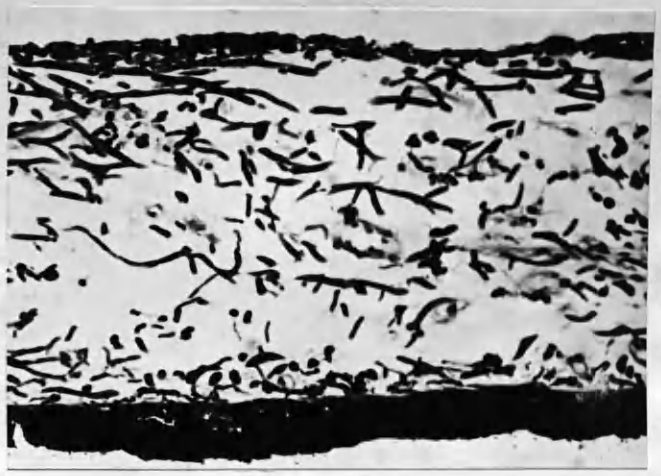

Fig. 25. MONKEY.

The stroma is of delicate texture. Chromatophores are numerous and have a twig-like shape.

THE IRIS.

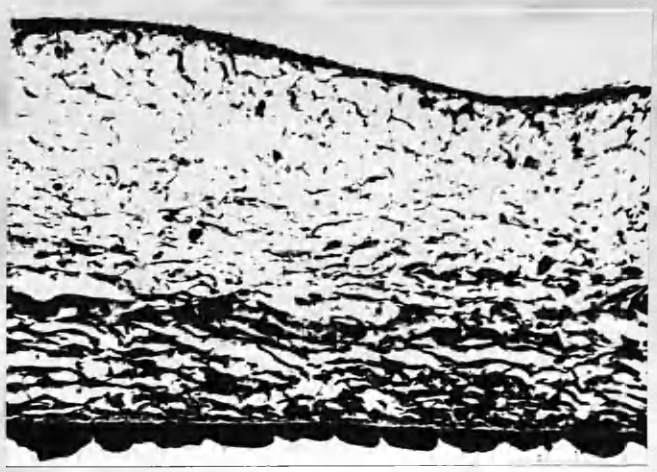

Fig. 26. DOG.

The chromatophores are numerous and have a twig-like shape.

THE IRIS.

Fig. 27. GOAT.

The stroma is dense. Chromatophores are scanty.

THE IRIS.

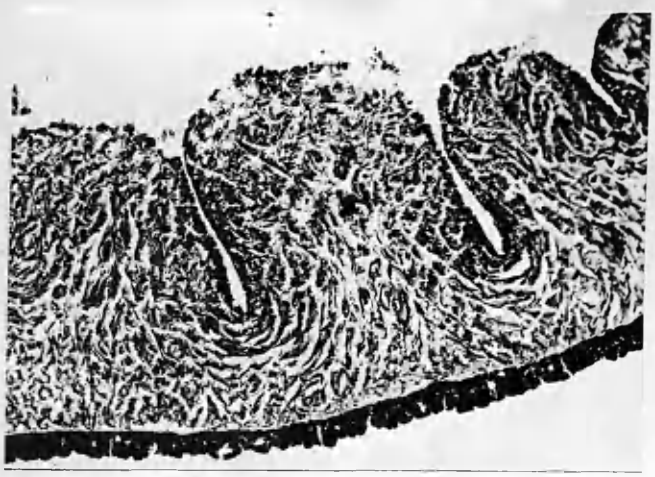

Fig. 28. HORSE.

The stroma is dense and chromatophores are numerous. Crypts are formed by folds in the surface of the iris.

UNDILUTED LIQUID NITROGEN MUSTARD GAS.

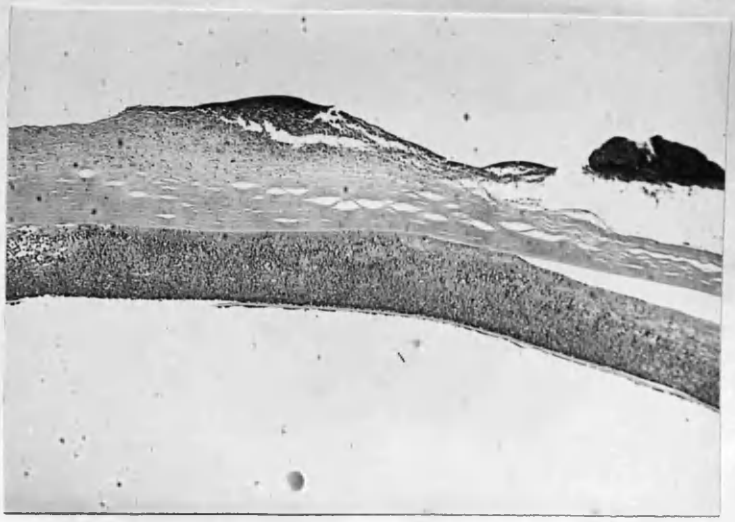

Fig. 29. RABBIT.

The corneal lesion at the 5th. day after a 1 mm. diameter drop dose. The cornea is necrotic and there is a relative absence of cell nuclei. The anterior chamber is full of cellular exudate, bounded posteriorly by lens capsule. The lens was removed before section was cut.

UNDILUTED LIQUID MUSTARD GAS.

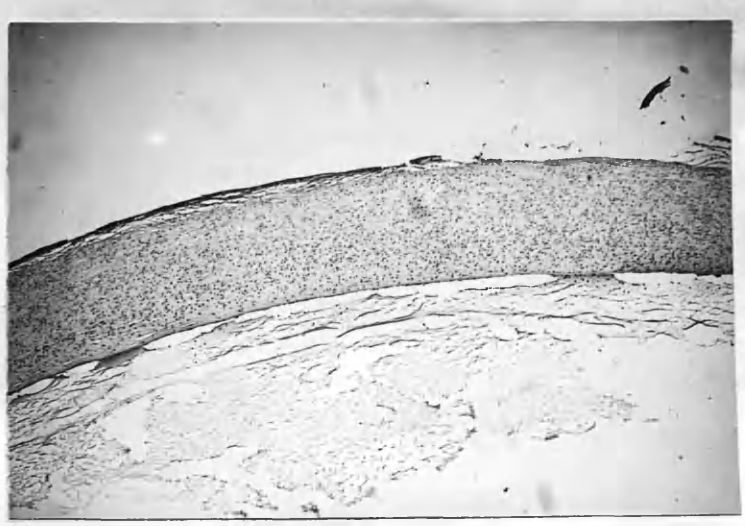

Fig. 30. RABBIT.

The corneal lesion at the 5th. day after a 1 mm. diameter drop dose. There is little loss of corneal tissue and the stroma is infiltrated with cells at all levels. The anterior chamber contains exudate which is mainly fibrinous in character.

1% AQUEOUS SOLUTION OF NITROGEN MUSTARD GAS.

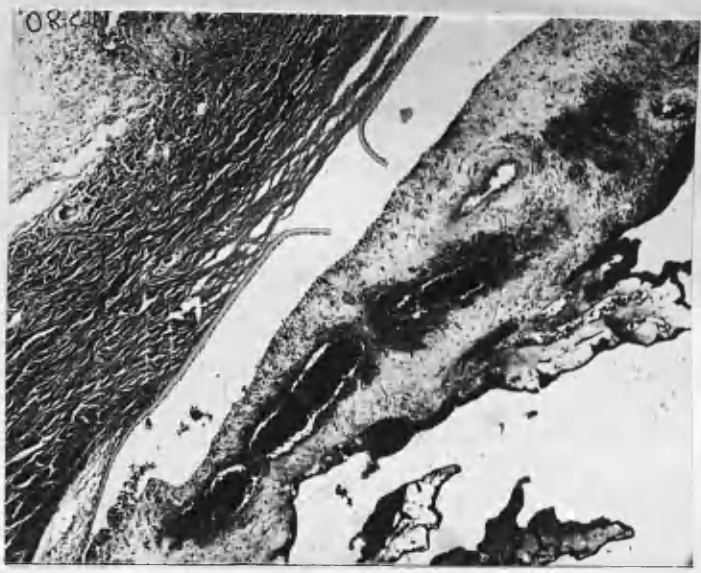

Fig. 31. RABBIT.

The early reaction in the iris after a non-destructive dose. The iris is grossly oedematous. The vessels are deeply congested and haemorrhages have occurred into the stroma surrounding the vessels.

UNDILUTED LIQUID MUSTARD GAS.

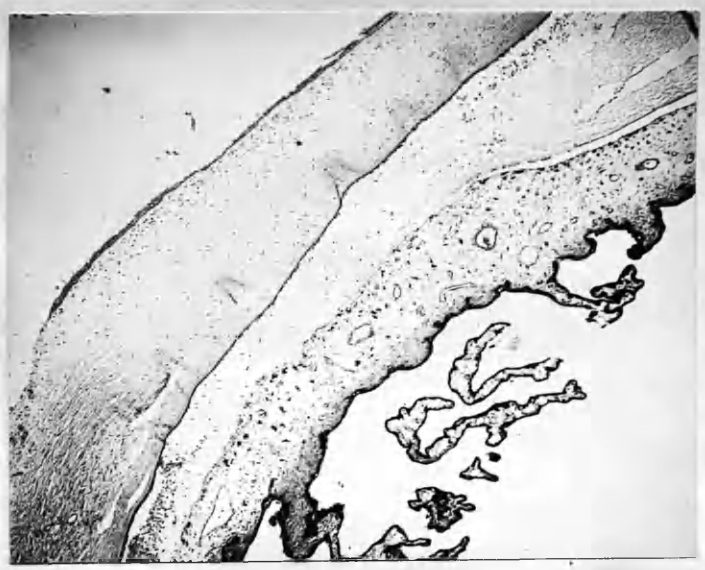

Fig. 32. RABBIT.

The early reaction in the iris after a destructive dose. The iris is slightly oedematous, but the vessels are not congested and there are no haemorrhages.

NITROGEN MUSTARD GAS VAPOUR.

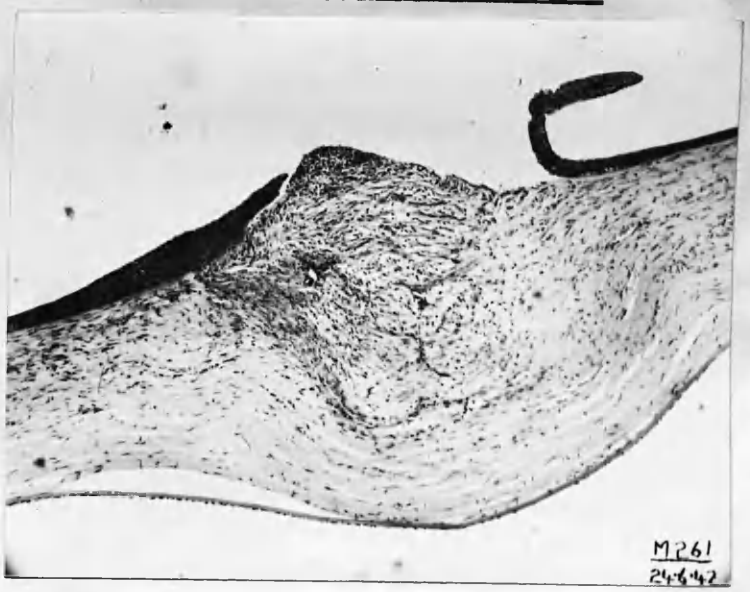

Fig. 33. RABBIT.

The corneal lesion at the 5th. week after a severe exposure to vapour. The epithelium is thickened near the lesion and is absent at its apex. A mass of degenerate material is being extruded from the anterior corneal layers, while the posterior region of the cornea is relatively little affected.

1% AQUEOUS SOLUTION OF NITROGEN MUSTARD GAS.

Fig. 34. RABBIT.

The early reaction in the iris. The vessels are deeply congested and haemorrhages are present in the stroma which is also very oedematous. The anterior chamber contains cellular exudate with a high proportion of red cells.

NITROGEN MUSTARD GAS VAPOUR.

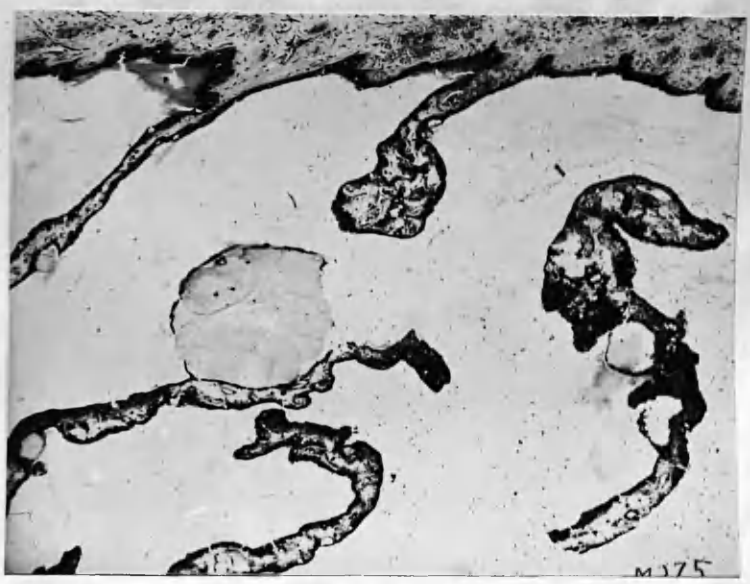

Fig. 35. RABBIT.

Vesicles formed in the ciliary processes in acute inflammatory processes. The vesicle is formed by separation of the neuro-epithelial layers and contains albuminous material.

NITROGEN MUSTARD GAS VAPOUR.

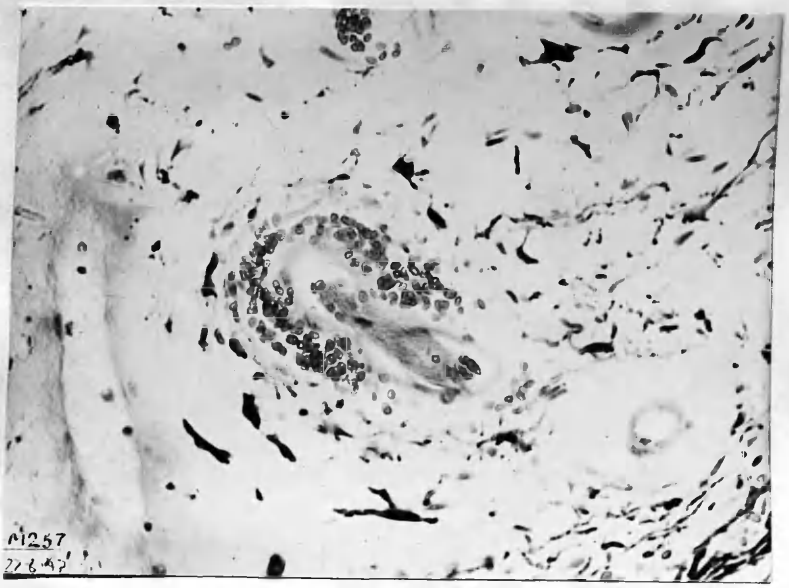

Fig. 36. RABBIT.

Thrombosis in a vessel in the iris.

NITROGEN MUSTARD GAS VAPOUR.

Fig. 37. RABBIT.

Atrophy of the iris. The iris is thinned, the stroma is of hyaline appearance with absence of cell nuclei. The chromatophores are swollen and rounded in form.

NORMAL TISSUES.

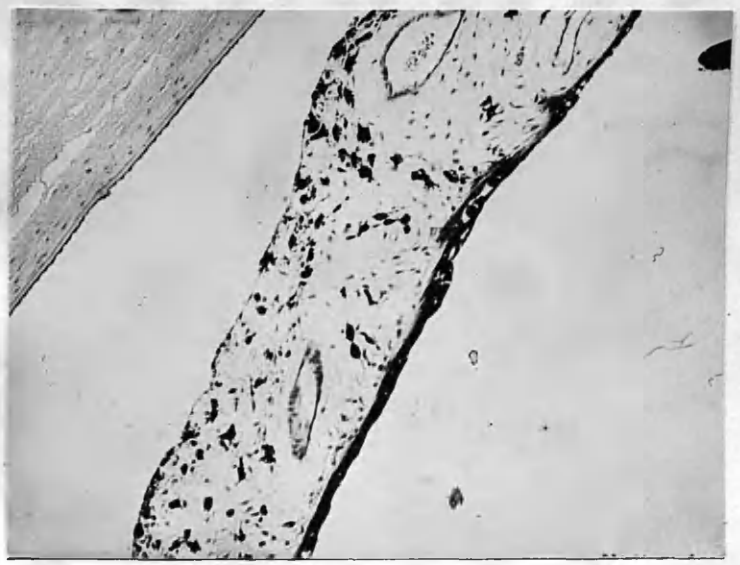

Fig. 38. RABBIT.

The normal iris for comparison with the atrophic iris shown above in the previous figure.

NITROGEN MUSTARD GAS VAPOUR.

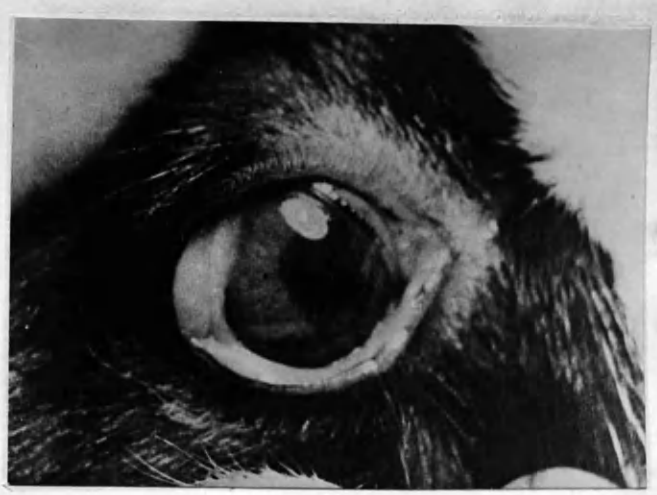

Fig. 39. RABBIT.

The appearance of the eye three months after a severe injury by nitrogen mustard gas vapour. The iris shows loss of surface markings.

MUSTARD GAS VAPOUR.

Fig. 40. RABBIT.

The appearance of the eye three months after a severe injury by mustard gas vapour. The iris shows normal surface markings.

NITROGEN MUSTARD GAS VAPOUR.

Fig. 41. RABBIT.

The iris shows loss of surface markings and is partially retracted downwards at the site of a previous large haemorrhage.

NITROGEN MUSTARD GAS VAPOUR.

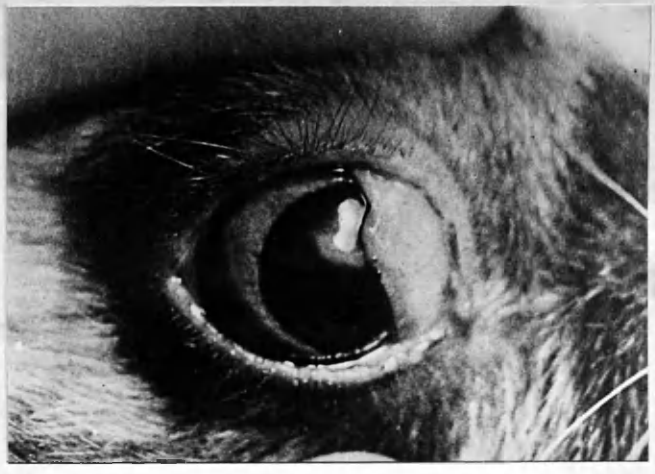

Fig. 42. RABBIT.

The iris shows loss of surface markings and is completely retracted downwards and forwards. There is a quiescent nebular scar in the cornea.

NITROGEN MUSTARD GAS VAPOUR.

Fig. 43. RABBIT.

Section of the retracted portion of the iris from the eye shown in Fig. 42.
The iris tissue is of hyaline appearance. A mass of organised fibrous tissue is seen on the surface of the iris near the angle of the anterior chamber.

THE EFFECT OF ATROPINE ON THE NORMAL EYE.

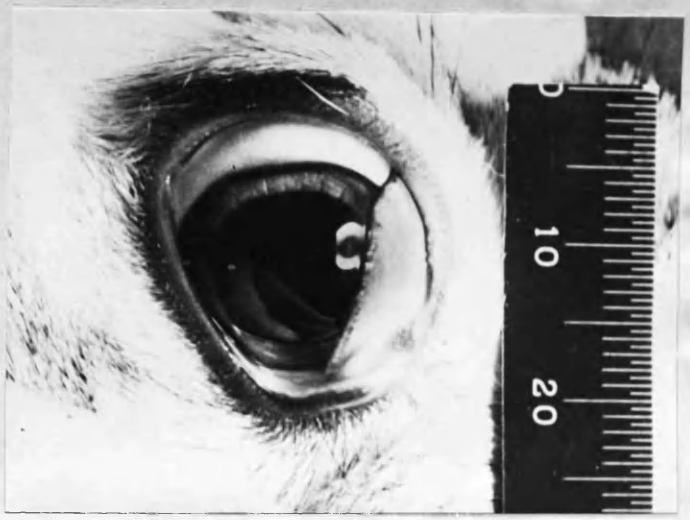

Fig. 44. RABBIT.

The pupil is fully dilated.

THE MIOTIC EFFECT OF LIQUID NITROGEN MUSTARD GAS.

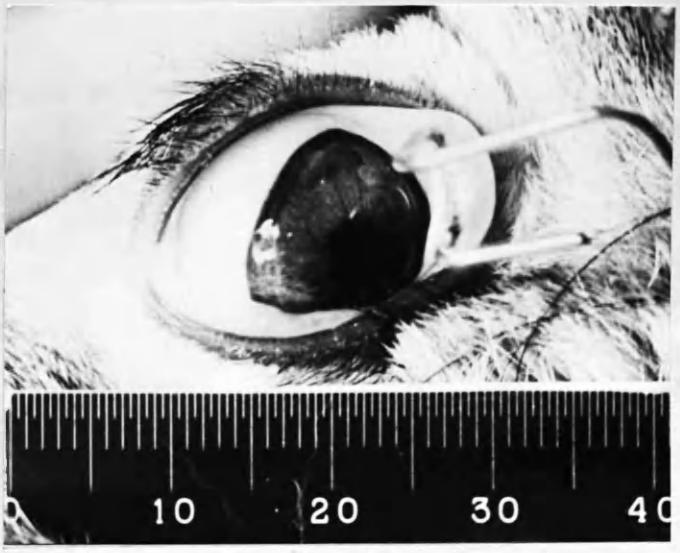

Fig. 45. RABBIT.

Nitrogen Mustard gas liquid has produced contraction of the pupil of the atropinised eye shown in Fig.44.

LIQUID LEWISITE TREATED BY B.A.L.

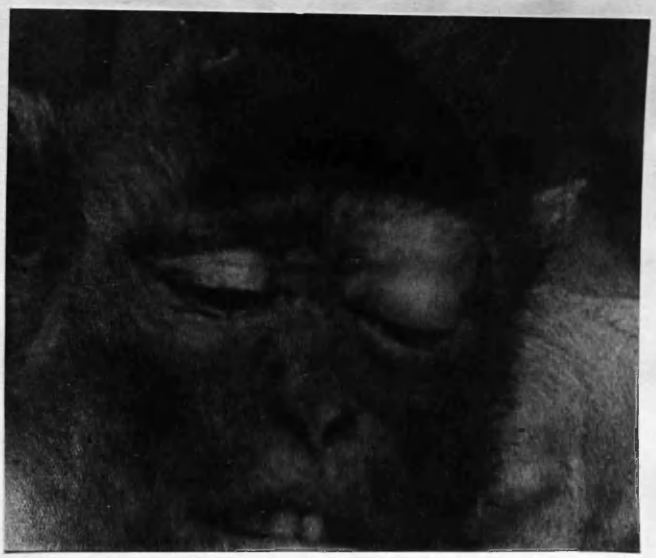

Fig. 46. MONKEY.

Condition 5 hours after injury. The antidote was applied to the right eye 15 minutes after injury. The left eye received a similar quantity of the inactive vehicle.

LIQUID LEWISITE TREATED BY B.A.L.

Fig. 47. MONKEY.

Same animal as in Fig. 46. Condition 30 days after injury. The treated eye is of normal appearance while there is a very severe lesion in the control eye.