ARTIFICIAL INSEMINATION

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The use of artificial insemination—i.e., the deposition of semen in the vagina, the cervical canal, or the uterus by instruments—has been discussed by several authors with personal experience of the method (Seguy and Vimeux, 1933; Lane-Roberts *et al.*, 1939; Cary, 1940; Green-Armytage, 1943; Guttmacher, 1942). We ourselves have used, and in certain respects developed, the technique of artificial insemination (A.I.) during the past five years. We can present but few conclusions in what must necessarily be a developing field, and cannot discuss the biological implications (e.g., determination of ovulation, frequency of male infecundity) of our observations in this interim report to clinicians. It is hoped, however, that it may serve to dispel certain misconceptions that are constantly arising.

Scope of Artificial Insemination

Impotence.—Many impotent husbands are capable of producing fecund semen by masturbation, and some impotent men regularly indulge in masturbation. Where treatment of impotence has failed, recourse to artificial insemination is indicated. Defects in the fecundity of the wife are first attended to. The physician then carries out an artificial vaginal insemination and Sims test (Barton and Wiesner, 1944) in order to determine the degree of cervical invasion by spermatozoa. Provided that invasion is adequate the wife is taught to carry out self-insemination within the fecund phase of the cycle (see below). The technique is as follows: She first douches with warm water (1 pint); half an hour later the husband passes semen into a cold dry glass container and allows it to liquefy at room temperature (about 10 minutes). The wife then draws up the semen into a clean dry urogenital glass syringe, and, lying on her back with knees drawn up, she passes the syringe into the vagina and very slowly expels the semen. The prone position should be retained for about half an hour. When teaching the patient it is important to demonstrate the distance to which the syringe may be inserted. The above procedure might suitably be employed in cases of hypospadias where insemination is superficial, but we have as yet had no such case under our care. Conception should occur readily. If it has not occurred within four or five cycles the case is reviewed. We have records of 11 selected cases. Eight pregnancies resulted in these. One ended in miscarriage; the patient conceived again subsequently and the pregnancy is progressing. Five pregnancies went to term. One other continues at present.

Dyspareunia.—In some cases of incurable dyspareunia (e.g., those developing after injury or operation) artificial insemination may present the only means of obtaining pregnancy. In our opinion A.I. should not be used in any case of dyspareunia unless persistent attempts at cure have failed; it should be remembered, however, that in some neurotics pregnancy itself may dispose of the disability. Vaginal self-insemination is the method of choice.

Failure to Ejaculate.—There are numerous cases, difficult to detect, in which the husband, though capable of penetration and sustained erection, either fails to ejaculate during intercourse or emits only a minute quantity of azoospermic fluid. In some of these cases ejaculation of fecund semen takes place during sleep. Where treatment has failed, the patient may be instructed to wear a washable condom during sleep, and the semen may be used for vaginal insemination, provided this is done immediately liquefaction has taken place.

Inadequate Cervical Invasion.—Sterility and reduced fertility are often associated with impaired cervical invasion by spermatozoa (Sims, 1868). Spermatozoa may be scarce in, or

entirely absent from, the cervical mucous plug, even though the sperm count and motility *in vitro* be high (Barton and Wiesner, 1944; Cary, 1940). We have found that spermatozoa which fail to invade the healthy cervical ovulatory mucus from the vaginal pool and are subject to rapid death in the vagina may under certain conditions survive for prolonged periods after transfer into the cervical canal. Furthermore, the occurrence of conception after deposition of asthenic spermatozoa in the cervical canal (first reported by Seguy) shows that the cervical mucus may maintain not only their motility but also their fertilizing capacity. The most critical task in the life of the asthenic spermatozoon appears to be penetration into the cervical mucus. No extended survival results from transfer into certain types of cervical mucus (e.g., those often seen in endocervicitis or in ovarian deficiency). Both experiment and clinical experience suggest that cervical insemination with the husband's semen (A.I.H.) should be used in cases of defective invasion, provided, first, that treatment of the male has failed to procure adequate invasive potency; secondly, that the spermatozoa show good initial motility; and, thirdly, that the cervical mucus during the ovulatory phase is clear and not gelatinous. More precise determinations (such as viscosity) can be made by *in-vitro* tests unsuitable for clinical routine. It should be added that impairment of invasion may be mechanical (e.g., malposition or abnormality of cervical passage), and some authors (e.g., Guttmacher, 1942) regard this condition as meriting artificial insemination.

Male Sterility and Other Indications for Artificial Insemination with Donated Semen (A.I.D.).—We have employed donated semen in a limited number of cases. In some of these (e.g., bilateral cryptorchidism, occlusion of ducts, fibrosis testis, incurable impairment of ejaculation) male sterility had to be regarded as permanent; in some others (e.g., extreme oligozoospermia) a condition of severe subfecundity had failed to respond to treatment, so that chances of conception were remote. In two cases biological considerations were decisive. In one of them deafness had recurred in three successive generations of the husband's family; in the other, transmissible nervous disease was established. Many other reasons have been advanced by patients requesting artificial insemination with donated semen (A.I.D.). Thus some couples, too impatient to submit to treatment, prefer the easy approach of A.I.D. This attitude is common in fecund women married to subfecund men. But quite often the husband is unwilling to undergo treatment, and the suggestion of A.I.D. comes from him. Some women demand A.I.D. without the knowledge of the infecund husband, claiming that paternity would save his self-esteem; such women are usually good and devoted wives who, having longed for children for many years of marriage, have rejected other ways of becoming pregnant. Others are impelled by different motives: e.g., they plan to force marriage by what they consider to be a guiltless conception. Neither these nor other more dubious reasons have been accepted by us; for while we do not feel in a position to suggest the general principles which should govern the application of A.I.D. we recognize the need for the greatest caution. In our work we have taken into account not only biological and medical factors but also the suitability of the couple for parenthood, so far as this can reasonably be estimated.

Procedure and Technique in A.I.H. and A.I.D.

Choice of Date

The wife is instructed how to record her rectal temperature throughout the menstrual cycle on waking; for as a rule the variations of the temperature not only reflect the two phases of the cycle (follicular and luteal respectively) but also indicate clearly enough the approximate date of ovulation (see Chart). Any intelligent woman, once fully instructed, is capable of recognizing the ovulatory phase by the low level and/or the peculiar prelude drop in the waking temperature. If this be indistinct in any cycle she should attend on the first day of the luteal rise. She is also asked to observe other signs of ovulation (Mittelschmerz, spotting, etc.). The final decision concerning the performance of insemination in any given cycle depends on the condition of the cervical plug, for if it is opaque the ovulatory phase is probably no longer, or not yet, in being. It should be borne in mind that even fecund women will

occasionally have a cycle with indistinct ovulatory signs, and in less fecund women this may be more frequent.

Chart of waking rectal temperature of an A.I.D. patient during only cycle under treatment. A: Day of artificial insemination. F: Day of positive Friedman test.

Insemination with Husband's Semen (A.I.H.)

We have found, in joint investigations with Dr. H. Coke (unpublished), that semen not infrequently carries pathogenic organisms which it would be unwise to deposit in the cervical canal. A bacteriological test is necessary in all doubtful cases (e.g., in sperm agglutination, pyospermia, haemospermia, etc.). Any infection should be attacked by local and systemic treatment of the husband. If these attempts fail the semen should not be used. Generally speaking, it is important to raise male fecundity to the highest possible level. Further procedure varies according to specific conditions. Where the main seminal deficiency consists in the lack of invasive power of a well-populated and viable semen the patients may be instructed to have intercourse half an hour after a thorough vaginal douche (warm water only). Semen may then be obtained from the posterior fornix within 60 minutes. The use of vaginal pools involves certain theoretical risks such as transfer of organisms from the vagina into the cervical canal. But some couples cannot adjust themselves to other methods of obtaining semen. The method is also valuable when it is undesirable, for psychological reasons, that the husband should be asked to masturbate repeatedly.

In cases of oligozoospermia and with semen of low viability masturbation specimens should be collected in suitable glass containers* just before insemination. The semen is used without additions and without any further manipulation except in cases of pronounced oligozoospermia, when it may be concentrated by gentle centrifugalization (approximately 500–1,000 revolutions per minute). In these cases the deposit is used with a small volume of supernatant fluid.

The patient is placed in the lithotomy position and the cervix, exposed by a dry unlubricated speculum, is swabbed with dry cotton-wool. A glass syringe fitted with an intra-uterine cannula or a special syringe of plated metal† is used, and a small quantity of semen (0.1–0.2 c.cm.) is drawn up into this syringe, which must be dry. As a result of certain still incomplete experiments we are under the impression that larger quantities of semen may impair the chances of intracervical survival of sperms. The tip of the cannula is passed into the cervical canal (1/4–1/3 in. of the external os). The semen is then injected *very slowly* into the canal. Most of the semen usually escapes from the cervix, but a small amount is retained. Forceful injection, recommended by Guttmacher (1942) and others, has neither an empirical nor a physiological basis; furthermore, it involves the risk of intra-uterine instillation. The patient may be allowed to leave a few minutes after insemination. Slight and passing discomfort sometimes follows cervical insemination; it is never severe, and may be disregarded.

It is an essential aspect of A.I.H. that it may have to be repeated frequently—i.e., *monthly* for a period of two years if necessary—before success is achieved or failure may be presumed. For the occurrence of conception is a matter of chance, though of high probability, even in fecund couples leading a normal married life. In infecund couples the chances

are small even though A.I.H. be used, hence repeated “exposure to risk” is indicated.

A.I.D.: (1) Selection of Donors

So far as we know, no organized collection of semen for donation has ever been established, and the provision of semen is therefore entirely in the physician's hands. This inevitably involves considerable difficulty in obtaining suitable material, but has the advantage that the physician knows the donor individually. Certain facile assumptions suggested by purely biological considerations must be refuted. Thus the husband's brother might be regarded as the first choice because of genotypical resemblance; but experience shows that this choice is usually incompatible with secrecy, and that it is conducive to emotional disturbances involving both husband and wife. In fact, the prospective parents should never be aware of the identity of the donor. We have come to this conclusion as a result of disturbing observations in cases where the donor (though biologically approved by us) was chosen by the couple. It would seem that the responsible donor and the maternal woman are emotionally too deeply involved in procreation to regard their relationship with detachment. Now we carry anonymity to the point where the donor is never described to the patient save in most general terms which exclude identification; nor does the donor receive any specific information concerning the recipients. But if he wishes to limit his donation to certain types of parents his wishes are, of course, considered. In view of requests and suggestions made by medical men and others it should be emphasized that in our opinion no specimen of semen should be used for insemination except with the explicit agreement of the donor.

The principles which govern the choice of donors are designed to reduce obvious biological dangers. There must be no history of transmissible disease; the family history of the donor must be free of adverse characteristics of possible genetical significance, such as alcoholism, criminality, or tuberculosis. Excessively pronounced physical features are undesirable not only because they may be objectionable themselves but also because they might facilitate identification of the donor.

Positive considerations concerning the eugenic quality of the donor's stock will largely be governed by the scientific views and perhaps the individual preferences of the physician concerned. Our choice has favoured men of intellectual attainments whose family history indicated that the members of at least two preceding generations were not only intelligent but also endowed with good capacity for social adjustment. Others might prefer donors characterized less by mental than by physical characteristics or achievements (athletes, etc.). In fact, we have hesitated before accepting cases for A.I.D. in which the interests of the parents were primarily athletic or sporting; and, speaking quite generally, the selection of donors with respect to the characters of the parents is a wide and complex problem. One has to bear in mind that the legal father may hope for a donated child with whose personality he might be in accord, and it must further be remembered that difficulties in the father-son relationship might be accentuated by the circumstances of A.I.D. Obviously, even the most careful choice of the donor for each case could not guarantee the desired characteristics, but it would increase the chances of matching parent and child. Present conditions make any such selection impossible.

The donor should have at least two legitimate children; this is of importance not only from obvious genetic considerations but also because his parental drive will have an available object. He must be of mature age (30 to 45), so that his character, viability, and other qualities can be properly assessed. His individual health should be adequate—primarily because it reflects constitutional characteristics. A certificate of the donor's physician is requested and a Wassermann test is carried out.

The fecundity of a donor must be reasonably high. The semen must have a volume of at least one c.cm., it must liquefy and rapidly become homogenous, the sperm count must exceed 30 millions per c.cm., and there must be no spontaneous agglutination. Viability must be high—1% after 100 hours at 4° C. The spermatozoa must show little variation

* Semen-containers and syringes should be cleaned without the addition of the usual antiseptics. They must be thoroughly dried before use.

† Supplied by A. J. Travis to our design.

of head-lengths and include less than 15% abnormal forms. Indifferent or intermediate and pathological cell-forms (e.g., di Biasi cells) must be rare. The bacteriological cultures obtained from the fresh semen must be sterile or show but a light growth of harmless contaminants such as *Staph. aureus* and diphtheroids. These requirements are dictated not only by the desirability of a high conception rate but also by the need to reduce the risks of miscarriage. Periodic checks upon the seminal conditions, etc., are made.

The donor's blood group should be identical with that of one parent if it is desirable to minimize the possibility of bastardization. The parents usually desire donors of like race—e.g., Jewish couples usually ask for a Jewish donor. On the other hand, it is a curious reflection on the present epoch that some have specifically asked for non-Jewish donors, since they want to safeguard the child so far as is possible against anti-Semitism.

The greatest difficulties in A.I.D. arise from the fact that to most balanced men the task of donation is unpleasant, and because of the low fecundity of most mature men. Hence but a very small panel of donors has been established so far. Fortunately, the number required at any given time is not great. For while a specimen of semen should not be used for more than a few hours after emission, it can during this period be utilized for at least 20 inseminations. In theory the number of possible conceptions from one specimen is very much higher, for we have satisfied ourselves that a single insemination with 0.01 c.cm. of semen may suffice to procure pregnancy. It follows that a fecund donor submitting two specimens weekly could, with ideal conditions, produce 400 children weekly (that is, about 20,000 annually).

A series of systematic observations has shown that A.I.D. has a good chance of success on any one of three cycle days—viz., on the day of the minimum waking temperature, on the day preceding it, and on the first day of the rise. Thus the general organization of A.I.D. requires an arrangement by which fresh semen is delivered to the laboratory two or three times weekly, while the recipients are asked to attend at the corresponding hours during the presumptive ovulatory phase. But while a small panel of donors can serve the immediate purpose, it seems desirable to limit the number of children any one donor should be allowed to have, lest the risk of marriage between sibs not known to each other should assume dangerous proportions. For this reason we have set an arbitrary limit of 100 children for each donor—not yet attained by any one donor.

The instructions given to a donor are simple, and are mostly concerned with delivery of the semen in a fresh condition without contamination. A sterile glass-stoppered container is supplied by the laboratory, and the specimen is maintained at room temperature. Donated semen is used for cervical insemination as described previously for A.I.H.

A.I.D.: (2) Preparation of Parents

A couple accepted for A.I.D. are made clearly aware of its biological, legal, and other implications and difficulties. Most couples have preconceived views concerning the method. Apart from believing that a single insemination on an arbitrary date is all that is required, they also assume that the husband can be nearly reproduced by a specially chosen donor. Hence they must be told that no likeness, physical or otherwise, can be guaranteed. The explanation of potential legal complications is based, in the absence of precedent, on counsel's opinion, for which we are indebted to our legal advisers. It is emphasized that the husband might change his attitude in years to come and attempt to disown the child. Both the possibilities and the difficulties of such attempts are pointed out. The couple are further informed that the child will be legitimate if the husband is registered as the father. Such registration is demanded although it constitutes an offence. For purely formal protection of the physician a written request for A.I.D., signed by husband and wife in the presence of the physician, may be obtained. This is filed under seal, and arrangements are made for the destruction of the document at the physician's death. The prolonged consultation required at this stage provides an opportunity to impress the couple once more with

the significance of their decision; and the physician can assure himself that the husband is not either acting on the spur of an ill-considered decision or submitting half-heartedly to his wife's request. On this as on other occasions an attempt must be made to establish the mutual confidence between patients and physician which is needed for their relationship and which is more important than any formal legal safeguard; the latter, in any case, could not cope with the numerous human complications which might arise in this field. Lastly, the patients are assured that complete secrecy will be observed.

Dangers

1. In our experience no dangers attach to the actual process of cervical insemination provided that no air is injected and no semen is allowed to enter the uterine cavity. But dangers may arise from the use of semen infected with pathogenic organisms, and while it seems that the healthy cervix is endowed with a defence mechanism against some semen-borne organisms it is not possible to detect impairments of cervical defence. At this point it may be remarked that we originally employed intra-uterine insemination as suggested by various authors. But on discovering the high incidence of seminal infection we abandoned this often painful procedure, which in the hands of an American author has resulted in grave injury (pelvic abscess and permanent subfecundity) (Bickers, 1944).

2. The question of dysgenic conception from the use of subfecund semen has often been raised—not only in the literature but also by patients who fear that the predominance of abnormal or asthenic sperms may be reflected in the constitution of the child. Now, this is indeed one of the most difficult problems in all animal-breeding, and yet one which has scarcely been formulated precisely—much less solved conclusively. It must be remembered that deliberate (experimental) damage to animal spermatozoa may not prevent conception but may result in non-viable zygotes, and that, in man, exposure of the father to some poisons has been stated to affect the offspring (Hamilton, 1925; DeLee, 1924). In human reproduction a close association of high miscarriage rate with semen of low fecundity has been claimed, and this association is indeed a common experience in the therapy of sterility: threatened miscarriage, usually at the end of the third month, occurs in more than one-third of the women who have conceived from subfecund semen. Cervical insemination might increase the incidence of non-viable progeny by interfering with the mechanism of cervical selection which inhibits the invasion of the cervix by abnormal spermatozoa. In artificial insemination the cervix receives many abnormal spermatozoa which could not invade under their own power. Much more experience must accumulate before the standard of the progeny of subfecund parents can be assessed properly. But it is encouraging that normal and viable infants were born in all our cases of A.I.H. in which pregnancy went to term without accidents of parturition or gestation. Also, the frequency of tubal pregnancy and other abnormalities of gestation was no greater than might be expected in a corresponding group of unaided conceptions.

3. A potential danger arises from the tempting chance of experiments with semen. Human sperms die fairly rapidly unless specific media are employed which can be used for storing semen. Again, infected semen can be disinfected without visibly affecting the sperms. Such procedures might simplify the task of artificial insemination, but we feel that interference with the semen carries the risk of affecting the progeny—a risk which may safely be accepted in animal-breeding but never, in our opinion, in human reproduction. Non-interference with semen should be carried to the point where storage or transport over long distances (which has been successfully used in America) is avoided. Artificial insemination should follow the natural course of events as closely as possible, and perhaps even centrifugalization should be regarded with reserve.

4. Lastly, there is always the danger of psychological damage to the patients, both husband and wife—e.g., either through the inevitable interference with their sexual relations or through the consciousness of reproductive inferiority. Careful initial selection of cases and attention to the patients' reactions can reduce this risk.

Results

For a variety of reasons no useful statistical analysis of the results of A.I. can yet be presented. The method and technique of A.I. have changed much during recent years—e.g., through the systematic use of the temperature chart—and the selection of cases has tended to become more stringent; the number of inseminations carried out before abandoning a case has increased, and so on. Hence results of earlier series are of little significance. Furthermore, in assessing the results of any given group, such factors as the age of the wife, the degree of male fecundity, etc., must be taken into consideration, and these vary greatly. The primary factor, however, is represented by the assessment of the case. Cases can be so selected that

A.I.H. will be successful in most, or in hardly any case, and the same applies to A.I.D. A few illustrations are given below:

1. *A.I.H.*—In a recent series of 30 successive cases A.I.H. was carried out because of low invasive power of the semen. In addition, spermatozoal density was low (less than 10 millions per c.cm.) in six cases; and more than 15% abnormal head forms were present in the semen of five cases. Female infertility factors—e.g., impaired tubal function, infrequent ovulation, etc.—were detected or strongly suspected in six cases. Insemination was carried out in at least four successive cycles where necessary and, as a rule, more than once in each cycle. One case is counted twice, for the patient miscarried after the first series of inseminations, and then made a second attempt. Nine conceptions occurred—in one case during the first cycle, in the others in the third or fourth cycle. Four pregnancies terminated in miscarriage in the fourth month of pregnancy or earlier; four others resulted in the birth of a viable infant. In the last case the pregnancy continues at the time of writing. In 21 cases no conception was recorded with certainty, but two conceptions may have occurred (? early miscarriage). The negative cases are characterized by a higher average age of the wives, but not by a higher frequency or greater severity of manifest infertility factors in either husband or wife.

2. *A.I.D.*—A recent series of 15 successive cases in which donor M. was employed consisted of women in whom no serious infertility factor was discovered, though four of them were 40 years of age or over. Insemination was repeated where necessary in at least six cycles. Conception resulted in 10 cases. The negative cases were represented by one woman in whom insemination was repeated during eight cycles and then abandoned, and the women aged 40 years or over. The fate of the 10 pregnancies varied. One was tubal and had to be terminated; one ended in miscarriage (end of the second month); five went to term uneventfully or are nearing term at present; and three terminated successfully at 45 weeks. The number of cycles during which inseminations were carried out in the positive cases varied from one to seven. It may be said that, in our experience, repeated A.I.D. is nearly always successful in reasonably young women in whom infertility factors have not been detected. The infants produced by donor M. in this as in another series show no abnormality and are progressing favourably. Their physical types vary widely, and the parents state in every case that they are glad to have availed themselves of this service.

Summary

In some cases of male impotence, dyspareunia, ejaculatory failure, and defective, cervical invasion, artificial insemination with the husband's semen may be indicated. In the first three conditions named, self-insemination by the wife is possible.

Artificial insemination with donated semen has been carried out in cases of incurable male sterility and for genetic reasons.

The procedure and technique of artificial insemination with the husband's semen and artificial insemination with donated semen (choice of cycle day, suitability of semen, method of cervical instillation) are described.

The selection of semen donors and the organization of artificial insemination with donated semen are discussed.

Some potential dangers of artificial insemination—e.g., uterine infection, dysgenic conception from defective or damaged sperms—are enumerated.

Two small series of cases are reviewed.

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A search for methods of controlling Scotland's "plague of midges" will be the task of a small committee of Scottish scientists headed by Brig. F. A. E. Crew, professor of public health and social medicine at Edinburgh University, and director of biological research at the War Office. Mr. Thomas Johnston, Secretary of State for Scotland, invited the committee to consider whether measures similar to those used in the Army against mosquitoes and other insect pests dangerous to health could usefully be employed against midges and other biting flies. The committee's first step will be to review what is known about methods of attack on insects and their breeding grounds and to advise whether these methods can be used or can be modified for use against midges.

METHYL BROMIDE POISONING EFFECTS ON THE NERVOUS SYSTEM

BY

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Methyl bromide (CH_3Br), a non-inflammable colourless gas at ordinary temperatures and pressures, fairly easily compressible into liquid form, is used extensively as an insecticide, fire extinguisher, fumigant, and refrigerant. It is known to be toxic to man in various ways, and as it is without smell in low concentrations and is 3.3 times as heavy as air it constitutes a very real industrial hazard. The toxic effects described in the literature are: (1) on the skin, giving rise to a vesicular irritative dermatitis and second-degree burns; (2) on the respiratory system, producing bronchitis, broncho-pneumonia, pulmonary congestion and oedema; (3) on the alimentary system, with gastro-intestinal upset and hepatic dysfunction; (4) on the nervous system, with both an acute and a chronic symptomatology. It is with the last that this paper deals, and although references show a familiarity with other manifestations, no attempt has been made to evaluate or define the more chronic effects on the central nervous system.

Review of Literature

Heiman (1944) has given a full review of the literature (chiefly Continental) concerning the general toxic effects of methyl bromide on man. An analysis of cases describing the acute neuropathies produced by short exposure to high concentrations shows in the majority a prodromal stage of headache, dizziness, nausea, vomiting, and generalized weakness with transient diplopia and amblyopia, followed by a period of mental excitement with focal or generalized epileptiform convulsions, muscular tremors and spasms, mental confusion, psychomotor acceleration, and restlessness, amounting at times to acute mania. This stage is accompanied by fever and occasionally cyanosis with methaemoglobinemia, and in fatal cases is followed by coma, increase in muscular spasms, and convulsive seizures with death in hyperpyrexia.

If the patient survives, there follows a long period of convalescence, lasting up to 18 months in a few cases, in which the epileptiform attacks become less frequent, the mental confusion and excitement gradually abate, and visual disturbances slowly improve, although nystagmus and sluggishly reacting dilated pupils persist, with mental depression and insomnia. Morbid hunger has also been described in this connexion.

Pathological material confirms the involvement of the brain and meninges in the acute type of case, but no reference is made to the spinal cord or peripheral nerves. Glaser (1928) described oedema of the brain with no further details. Goldschmid and Kuhn (1920) found degeneration of the cortical cells in the cerebral hemispheres, particularly in the frontal and parietal lobes. Duvoir (*et al.*, 1937; 1939) found acute congestion of the brain and meninges, and Heiman decrease of cerebrospinal fluid, swelling of the brain with engorgement of pial veins but no haemorrhages. The brain was found to contain traces of methyl alcohol and formaldehyde, and 62 mg. of bromide in 300 g. of tissue. No microscopical findings were mentioned.

The neurological effects of long-continued exposure to small concentrations have been described in only a few cases, and no pathological material is available, except from animal experiments. Jacquet reported one case with vertigo, weakness, transient diplopia, and dimness of vision following brief exposure, and two cases with similar symptoms plus flaccid paralysis of legs and psychic disturbances after more prolonged exposure to an unknown concentration. Watrous (1942) much later reported the occurrence of mild nervous symptoms in 31 persons out of a total of 90 working in a filling-and-sealing room of a methyl bromide plant who were exposed for two weeks to a concentration of less than 35 parts per million. Headache, vertigo, difficulty in focusing, muscular pains, and dimness of vision were the symptoms observed, but no neurological abnormalities were found on examination. All these cleared up within two months of the patients' leaving the factory.