remain effective for a long time. These are difficult conditions to satisfy, and it is clear that many methods of applying D.D.T. are inefficient. With porous materials D.D.T. is absorbed away from the surface and becomes unavailable; it is therefore difficult to render such surfaces insecticidal.[6 7 9 17] A possible remedy is to apply the D.D.T. in the form of an emulsion rather than a kerosene solution,[18] or, better still, as an aqueous suspension which leaves the insecticide deposited superficially.[19] Some useful emulsion concentrates have been described.[20 21] Loss of toxicity from walls may be due perhaps to cleansing operations[22]; loss from the hides of treated cattle appears to be due mainly to them licking themselves.[23] In both cases the residual action can be prolonged to some extent by adhesive agents used with the insecticide.[3 24]

There is disagreement on the exact type of deposit required for maximum insecticidal action. Some workers have found small crystals most active,[3 6] others say that size is unimportant,[26] yet others report that the larger crystals are most toxic.[25] Again, it has been noted that D.D.T. crystals are more toxic than supersaturated solutions[26]; but in another investigation dry crystals were made more toxic by spraying with plain oil.[6]

Interesting results have also been obtained with numerous analogous compounds tested on various insects[27] and on white mice,[28] and these results may have some bearing on the problem of the mode of action of D.D.T. Progress has also been made in determining the physiological effects of D.D.T. on insect metabolism.[29 30] Finally, the most important problem in the field of vertebrate poisoning with D.D.T. is the effect of long-continued small doses. One report is already available[31] and further work is known to be in progress.

TRANSFUSION PRECAUTIONS

Since the end of the war the E.M.S. Transfusion Service in England and Wales has been continued as the National Blood Transfusion Service, and a measure of its need is the increase shown in all its activities during 1946 and 1947. To take two examples—the demands for stored blood in 1947 were greater than in 1946 by some 50,000 bottles, and the issues of dried plasma also showed a considerable increase, rising by some 10,000 bottles. In Scotland the Scottish National Blood Transfusion Association has carried on the service it set up during the war, and in Northern Ireland a transfusion service on the lines of the National Blood Transfusion Service is being established. More blood and plasma are being used now than during the war. Generally, the wider use of transfusion is commendable, for previously many patients who would have benefited were not transfused. On the other hand, blood and plasma are potentially dangerous fluids unless prepared, stored, chosen, and used with extreme care.

The relative profusion of these fluids may be dangerous if the simple but important points to be observed in their use are neglected, if the need for the often complex investigations demanded by modern knowledge of the blood groups is not realized, and if the possible harmful, and sometimes tragic, results of transfusion are not considered. Dr. J. Wallace and Mr. R. D. Richards bring out a number of these points in their article in this issue. They confirm previous observations that properly collected and refrigerated stored blood is no more productive of reactions than fresh blood. Six of the nine reactions they report are attributed to the use of long-stored sterile giving sets, an event which may occur in any blood bank unless there is close supervision and a steady turn-over. Without constant supervision stored blood itself may be overlooked in the refrigerator and used after the normal expiry period of 3–4 weeks. In fact, blood stored for much longer than this has been transfused.

The wider understanding of the implications of the Rh factor has increased the need for care in the use of blood. Intramuscular and subcutaneous injection, as well as the transfusion of Rh-positive blood to Rh-negative recipients, can cause immunization which is permanent and may have serious results. It is essential that only Rh-compatible blood be given when transfusing any female of child-bearing age or younger, and all women who have been pregnant. Ideally, in males and nulliparous females past the menopause Rh-compatible blood should also be used; at any event an Rh-compatibility test should be made if such people have previously been transfused. The simple expedient of always giving only Rh-negative blood cannot, however, be accepted as a solution of the problem, because it would be wasteful of supplies which are naturally limited and should be reserved for Rh-negative cases. Only in emergencies should the Rh grouping be omitted and Rh-negative blood used irrespective of the Rh group.

It seems established that the transfusion of plasma or serum may be followed in up to 10% of cases by the development of hepatitis, which is sometimes fatal and is indistinguishable from infective hepatitis save for its long incubation period of some 40–120 days. Two such cases have recently been reported in this *Journal*.[1 2] This risk must always be considered when the use of plasma is contemplated, and plasma should be given only when the benefits likely to accrue from the transfusion outweigh it. Until the various methods now being investigated of destroying the infective agent have been shown to be effective, or a laboratory test to detect infected plasma has been developed, the only methods of control are the withdrawal of batches of plasma shown by transmission of the disease to be infected, the preparation of plasma from small pools, and the rejection of donors with a recent history of jaundice. All plasma now being dried in England is made from pools containing not more than the plasma from 10 bottles of blood, but there is much plasma made from larger pools still in use. The prompt withdrawal of infected material will depend upon the possible association in the clinician's mind of hepatitis with transfusion of plasma, upon the reporting of such cases to the Regional Transfusion Centre, and upon the accurate recording of bottle numbers in the case notes of all patients given plasma. Too often when cases of homologous serum jaundice are reported it is found that no such record has been made.

Constant and close supervision of the use of blood and plasma is required, and in large hospitals at least there would seem to be the need for the appointment of a transfusion officer to supervise not only the administration of the blood bank provided by the Transfusion Service but also to perform the necessary and often complex tests to ensure compatibility and to make any subsequent investigations. The Regional Transfusion Centres can perform much of this work, particularly for the hospitals in their vicinity or for hospitals having no laboratory, but they cannot, even if they wished, carry out all the tests and investigations which should be made in their regions. The appointment of resident clinical pathologists in larger hospitals would seem to be the best way of solving this problem.

[1] Scott, K. B., and Tovey, G. H., *British Medical Journal*, 1948, **1**, 196.
[2] Apley, J., and Wallis, H. R. E., ibid., 197.

HUMAN CHORIONIC GONADOTROPHIN

In 1939 Astwood and Fevold[1] reported evidence which suggested that the anterior pituitary secretes three rather than two gonadotrophic factors. The first of these (FSH) stimulates the ovarian follicle to ripen, the second (LH), acting after and in conjunction with FSH, causes ovulation and initiates luteinization, whilst the third (luteotrophin) is said to be essential for the maintenance of the formed corpus luteum. As none of the pituitary hormones have been isolated, and as they are not available in adequate amounts for therapeutic purposes, various anterior-pituitary-like substances of chorionic origin are employed instead. Chief among the latter are equine serum gonadotrophin, which is follicle-stimulating, and human pregnancy urine gonadotrophin, the action of which has been the subject of controversy. In laboratory animals it is mainly luteinizing, but its effect on the human ovary is doubtful, and M. E. Davis[2] goes so far as to state that it "does not affect the human female favourably so that it is probably of no value in gynaecological therapy." This is an extreme view, but certainly human chorionic gonadotrophin when given alone has never been shown to possess the property at one time attributed to it of inducing ovulation and of initiating luteinization in woman. However, an investigation controlled by hormone assays and endometrial biopsies into the possibility of inducing ovulation in the human by a combination of follicle-stimulating hormone and chorionic gonadotrophin—the "one-two cyclic gonadotrophin therapy" of Hamblen and C. D. Davis[3]—gave promising results in a small series of cases. Other workers have failed to confirm these findings, but it is possible that the conflicting results may to some extent be due to variations in the dosage, purity, and potency of the preparations used.

Further light has now been shed on the subject by Brown and Bradbury,[4] who describe a controlled study of the physiological action of chorionic gonadotrophin in normal women. In four cases the daily injection during the secretory phase of the menstrual cycle of amounts varying between 5,000 and 20,000 international units of the hormone produced a state of pseudo-pregnancy for periods of up to 19 days. Biopsy in these cases revealed the presence of decidual changes in the endometrium; the urinary excretion of pregnanediol continued beyond the usual life-span of the corpus luteum of menstruation; and in one case a well-developed and active corpus luteum was demonstrated at laparotomy on the fourteenth day of treatment. The onset of menstruation, however, could not be delayed indefinitely in these cases, bleeding occurring during, and despite, uninterrupted treatment. No explanation is offered for this last phenomenon, but it may lie in the fact that Brown and Bradbury gave the same dose daily in each case, whereas progressively larger doses may be required to maintain luteal activity. Once menstruation had begun the injection of the hormone was without effect. A more significant finding was that in five individuals treatment during the follicular phase of the cycle did not appear to hasten ovulation or the onset of luteal function. These observations strengthen the suggestion previously made that while chorionic gonadotrophin prolongs the activity of a pre-existing and functioning corpus luteum it does not by itself induce ovulation or initiate luteal activity. This view does not necessarily confirm the theory that there are three pituitary gonadotrophins, but if there are, then chorionic gonadotrophin resembles in its action luteotrophin rather than LH. It also follows that it should be used when it is desired to enhance already established but deficient luteal activity. This is not to deny that chorionic gonadotrophin may have other uses. Thus it is sometimes of value in the treatment of metropathia haemorrhagica where there is a complete absence of luteal activity, but in such cases there is some reason to believe that it controls the bleeding not by stimulating corpus luteum function but by depressing follicular activity.

[1] *Amer. J. Physiol.*, 1939, **127**, 192.
[2] *Progress in Gynecology*, 1946, p. 203. Edited by J. V. Meigs and S. H. Sturgis. New York: Grune and Stratton.
[3] *Amer. J. Obstet. Gynec.*, 1945, **50**, 137.
[4] Ibid., 1947, **53**, 749.

THE TREATMENT OF CHOLERA

Hopes that the commoner sulphonamides or antibiotics would be active against cholera were disappointed. Bhatnagar and his colleagues,[1] however, have now produced a compound which in preliminary trials seems to have been much more effective. The first observation was that hexamethylene-tetra-amine in a 10% solution in physiological saline would kill cholera vibrios *in vitro* in less than half an hour. Crude compounds in which hexamine was linked with sulphanilamide were then prepared and in preliminary experiments gave promising results in animals and man. Later a condensation product containing two molecules of sulphathiazole and three molecules of formaldehyde was made. This compound has the formula $C_{21}H_{22}O_6N_6S_4$, but its actual constitution has not yet been worked out: for the present it is termed Compound 6257. *In vitro* bactericidal action on cholera vibrios was well marked in concentrations of 50 mg. per 10 ml., while with lesser concentrations above 5 mg. per 10 ml. there was bacteriostatic activity. The *in vitro* tests were confirmed in mice inoculated intraperitoneally with 2 M.L.D. of cholera vibrios. When mice were given 40 or 50 mg. in divided doses for two days prior to inoculation and then the same dose morning and evening for four days after inoculation there was complete protection if the drug was given subcutaneously or intraperitoneally. If given by mouth the drug saved only 10% of mice, presumably because of poor absorption from the alimentary tract.

Field trials were carried out in the Tanjore District of Southern India. The patients were for the most part undernourished women and children suffering from the effects of purgation, vomiting, and suppression of urine. A specimen of stools was first examined to establish the diagnosis, and the drug was then given in a dose of 6 g. followed 4 hours later by 4 g.—usually by mouth, though if vomiting were profuse the drug was administered per rectum. As a rule the total dosage was 28 g., of which 10 g. was given on the first day, two doses of 4 g. on the second day, and thereafter two doses of 1 g., morning and evening, for the next five days. Under this regime vomiting ceased and purgation was reduced within six hours: the urinary output was normal in about nine hours. Cholera vibrios were absent from the stools by the fifth morning.

So far 85 cases of bacteriologically proved cholera have been treated under field conditions in 27 villages, with a mortality of only 4%—in contrast to the usual mortality during the past seven years of 60%. No toxic manifestations have been seen even when as much as 50 g. has been given. Plenty of water, however, was drunk by the patients, and soda water when available. Although no details are given, it is said that the drug has been remarkably effective when administered prophylactically to contacts living in infected villages. If these results are confirmed a considerable advance in the chemotherapy of cholera has been made.

[1] Bhatnagar, S. S., Fernandes, F., De Sa, H., and Divekar, P. V., *Nature*, 1948, **161**, 395.

BITING MIDGES IN SCOTLAND

The minute black midges of the family *Ceratopogonidae* are very common in parts of Scotland during the summer months, particularly in the West Highlands, where the indignant sportsman frequently blames them for the lost salmon or the missed grouse. They do not transmit human diseases in this country, but most people who are bitten find the consequences very unpleasant. The irritation from the bite begins at once and may continue for several days; scratching aggravates it and may cause secondary infection. Nor do bites come singly: it is estimated that there are at least 50,000 active midges to the acre in areas where they are abundant. Investigations in the Trossachs at the height of the midge season (July–September) have given averages of 150 midges per person per hour. It is not surprising that agricultural work has been seriously impeded by midges in some places, and that the tourist traffic has suffered in the summer months.

A few years ago the subject of midge control was made the study of a special committee of the Scottish Department of Health. In 1946 an interim report was issued,[1] and recently a second report has appeared.[2] The most important item in the first report was the recommended use of the repellent dimethyl phthalate[3] as a protection against midge bites. Biological data were few, and existing records showed the difficulty of direct control measures. The midges belong to the genus *Culicoides*, of which fifteen species were found; most of the trouble was clearly due to one species, *C. impunctatus*.

The recently published report contains details about the methods adopted to obtain further information about the life history of the midges. A trap was made in the form of a box, and in the bottom and sides of this small glass vials were inserted. Traps of this type were inverted over likely breeding-grounds, and the emerging midges were attracted by light into the glass vials. By this means some information has been obtained about the types of breeding-sites chosen by different species. Unfortunately relatively few of the most important species were caught in the traps, so that their preferences are still uncertain. When the breeding areas are known it may be possible to render them unsuitable or unattractive by drainage or similar operations. Alternatively it may prove feasible to attack them with insecticides. In the meantime sufferers will have to rely on the DMP (dimethyl phthalate) repellent. Further trials have confirmed its value. It can be applied to the skin—various formulae are suitable, but they must contain at least 40% of the substance. Skin applications only remain effective for a few hours, but more prolonged protection is possible by using wide mesh (4/16 in. × 5/16 in.) veils impregnated with DMP. These are worn over the head and give protection without obscuring vision. If kept in a tin when not in use they remain effective for a fortnight.

COPENHAGEN INSTITUTE FOR HUMAN GENETICS

The foundation of an Institute for Human Genetics at the University of Copenhagen was first proposed by Prof. Oluf Thomsen in 1935. In 1938, with the help of a grant from the Rockefeller Foundation, the Institute was established, Prof. Tage Kemp being its first head. There is no doubt that had this department not existed it would have been necessary to create it in order to meet an urgent need. During the years 1929 to 1939 several eugenic laws were adopted in Denmark. These dealt with sterilization, prohibition of marriage in certain circumstances, and abortion on eugenic grounds. The laws were skilfully framed and provided ample safeguards; they might well serve as a model for study should similar measures be contemplated in this country.

In a recent account[1] given to the Eugenics Society Prof. Kemp explained the working of the system and its practical results. It is not claimed that the new laws are having any great effect on the population as a whole. The aim has been different—the humane and intelligent application of measures to the benefit of the individual patient. To quote Prof. Kemp: "It is sometimes stated that the main purpose of eugenics is to spare society a good deal of expense. This, of course, is a great mistake. Negative eugenic measures are of an entirely medical character, aiming at the prevention of disease and misfortune." The average annual number of sterilizations was less than 20 in 1929–34, rising to 280 in 1935–9, and was no more than 350 during the years 1940–5. The use of these laws and the operation of the medico-legal machinery which they set up created the demand for genetic advice, and this the University Institute has been well qualified to supply.

During its brief life the research record of the Institute has been magnificent. In some ways the war almost helped research in Denmark; at least research was not interrupted to anything like the same extent as in many other countries. The Danes had no armed forces in which to serve. So far as they could they ignored the German occupiers and for long periods could concentrate on their work. We in this country can also be grateful because, presumably to annoy the Germans, English became the standard medium of publication. Apart from one volume in Danish (with English summary), all the wartime publications of the Institute are in English. From 1941 to 1946 ten large volumes of *Opera*[2] have appeared. Two of these are bound collections of reprints; the others deal with the following subjects: Graves's disease, achondroplasia, harelip and cleft palate, gipsies in Denmark, haemophilia, pituitary dwarfism in mice, deaf-mutism, and cancer of the breast. The attempt was being made, apparently with success, to ascertain and study every case of the rarer of the above diseases in Denmark. The material is carefully analysed and the conclusions fully set out. But what is even more valuable is that the individual case histories are given in detail, so that these volumes will remain an admirable source of material for research workers for many years to come. It was only after the war was over that the *Opera* became known in this country. Accordingly we propose to deal with some of them in a series of annotations. The first, on haemophilia, will appear in a later issue.

Prof. Warren H. Cole, M.D., F.A.C.S., Professor of Surgery in the University of Illinois, will deliver a Moynihan Lecture before the Royal College of Surgeons of England (Lincoln's Inn Fields, London, W.C.) to-day (Friday, April 2) at 5 p.m. His subject is "Repair of Strictures of the Common Bile Duct."

Dr. F. J. Nattrass, F.R.C.P., will deliver the Lumleian Lectures before the Royal College of Physicians of London (Pall Mall East, S.W.) on Tuesday and Thursday, April 13 and 15, at 5 p.m. His subject is "Clinical and Social Problems of Epilepsy."

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[1] *Control of Midges*, 1946. Edinburgh: H.M.S.O.
[2] *Second Report on Control of Midges*, 1948. Edinburgh: H.M.S.O.
[3] *British Medical Journal*, 1945, **1**, 705.

[1] *Eugen. Rev.*, 1947, **38**, 181.
[2] *Opera ex Domo Biologicae Hereditariae Humanae Universitatis Hafniensis*, Copenhagen, Ejnar Munksgaard.