Fuels," Dr. Ormandy and Mr. D. Ross dealt with the use of alcohol as a motor fuel when mixed with petrol or benzol. Alcohol has the great advantage that it allows the use of a much higher compression ratio in the engine than petrol or any constituent of petrol, thereby obviating premature detonation (' pinking '). Commercial (95 per cent. vol.) alcohol does not mix well with petrol, but now that alcohol can be easily and economically dehydrated by distilling azeotropic mixtures, this difficulty has disappeared. Road tests carried out by the London General Omnibus Co. using petrol with a small proportion of 99 per cent. alcohol, and a mixture of 65 per cent. denatured alcohol, 30 per cent. benzol, and 5 per cent. ether gave quite satisfactory results and showed that, owing to its anti-detonating action, alcohol can advantageously be added to low-grade petrols to improve their value.

The great importance of the size of particles of pigment and compounding powders used in the paint and rubber industries, was discussed at a conference presided over by Sir William Bragg. After Dr. D. F. Twiss and Mr. C. A. Klein had outlined the main problems, specialised papers were read by Dr. S. S. Pickles, Dr. P. Schidrowitz, Mr. T. R. Dawson, Mr. Nöel Heaton, Mr. E. A. Murphy, Mr. H. Green (U.S.A.), and by Messrs. G. Gallie and B. D. Porritt. At the concluding sessions Mr. L. J. Simon and Prof. J. W. Hinchley contributed a paper on fat-extraction by solvents, in which they described a new large-scale process for extracting fat from seeds which involves a very short period of extraction, economy in the consumption of solvent, and low capital cost; and Dr. E. W. Smith presented a very useful summary of recent discussions concerning solid smokeless fuel. Low-temperature processes, said the author, are at present both technically and economically unproven and the immediate problem consists in improving high-temperature coke for industrial and domestic uses. Such coke must be dry, and contain as low an ash-content as is compatible with economic production. It must be suitably graded, and the grades standardised.

The attendance at all the conferences was very good, and the papers were of a high standard, although there were so many of them that little time was left for discussion. Considered as a whole, the meeting was remarkable not only for its magnitude, but also for the diversity and interest of the subjects discussed.

The Commercial Production of Hormones.

AT a joint meeting of the Biochemical Society and the London Section of the Society of Chemical Industry on July 20, a series of papers on "The Scientific and Industrial Problems presented by the Hormones—the Natural Drugs of the Body," was read. The chair was taken by Sir Alfred Mond, who, in the course of his introductory remarks, referred to the work done by the British school on this subject and to the success which has followed the co-operation of the biochemist, the manufacturer and the physiologist, especially in the commercial production of insulin. The financier, though doubtless an essential member of the team, should occupy a subsidiary position to the research worker. Dr. H. H. Dale followed with a paper on the experimental study and use of hormones; Dr. H. W. Dudley described the chemistry of the pituitary gland and of insulin, and Mr. F. H. Carr the commercial production of hormones; Dr. H. A. D. Jowett gave an account of the history of adrenaline, and Prof. G. Barger discussed the recent progress in the chemistry of thyroxine. Dr. J. W. Trevan's paper on the biological assay of hormones was not read, but in the following account of the main parts brought out by the various speakers, use has been made of an abstract with which we have been furnished.

Only one of the hormones has, so far, been synthesised in the laboratory. Although the presence of a pressor principle in the suprarenal gland was first shown by Oliver and Schafer in 1894, it was not until 1901 that it was obtained in the crystalline state by Takamine, who, with greater courage than was shown by previous investigators, added strong ammonia in excess to the purified aqueous extract of the gland and so precipitated the base. In the same year Aldrich assigned it the formula $C_9H_{13}O_3N$, and this was afterwards confirmed: its structure was definitely proved by Jowett in 1904, who, by exhaustive methylation and subsequent oxidation, obtained veratric acid and trimethylamine, and about the same time the compound was also synthesised by Stolz. The synthetic product was of course the racemic form: in 1908 Flacher separated the dextro- from the lævo- variety, by treating the bitartrate with methyl alcohol, which dissolves the former and leaves the latter behind. The pressor effect of the lævo- naturally occurring form is fifteen times greater than that of its isomer.

Although the chemist may have finished with adrenaline, to the biochemist and physiologist it is still the central figure in many unsolved problems. How does the body make it? What is its function under ordinary conditions of life? To the first question there is as yet no answer: to the second a tentative reply may be given, but it is a curious fact that, although adrenaline has so simple a chemical constitution, and such a powerful physiological action when injected, yet its presence in the body under ordinary conditions, except in the suprarenal glands themselves, has been extremely difficult to demonstrate satisfactorily: in fact it has even been denied that it has any function in ordinary circumstances. It is probable, however, that it plays a part in the maintenance of the tone of the small blood-vessels, and also is secreted into the blood stream in larger quantities under conditions of emotional and physical stress.

It is interesting to contrast with the history of adrenaline that of thyroxine. The administration of thyroid gland in myxœdema was the first example of a successful substitution therapy: it is still the main example of this type of treatment, and, excepting possibly the oxytocic principle of the pituitary gland, the only example of a successful result being obtained by administration by the mouth. It is stated to have been used in China for this purpose more than a thousand years ago. But the active principle was not isolated until a few years since, when Kendall was successful in preparing it. Within the last year Harington has been able to synthesise desiodo-thyroxine, the compound formed when the iodine is removed from the molecule of thyroxine. An account of Harington's work has been recently given in these columns (July 10, p. 65), so that it will not be further discussed here: it may be assumed that the final synthesis is now only a matter of time.

The commercial production of other hormones, of which the chemical constitution is unknown, requires the supervision of skilled chemists in the process of manufacture, and the co-operation of the research biochemist in the improvement of existing processes or the discovery of new ones; the physiologist is also required, since the detection of the presence of the hormone and its quantitative estimation require the use of animal tests in the absence of satisfactory chemical reactions. The usefulness of this co-operation has never been more successfully shown than in the commercial production of insulin. At the present time firms in Great Britain satisfy all home requirements, and have a large balance available for export, whilst the price is low enough to bring the remedy within the means of the poorest diabetic. Of the hormones of, at present, unknown chemical constitution, insulin and those of the posterior lobe of the pituitary gland are the best known. Secretin, the hormone which arouses the secretion of pancreatic juice at the inflow of the partially digested food from the stomach into the duodenum, from the mucous membrane of which it is absorbed into the blood stream, has been recently obtained in a very pure form by J. Mellanby. The active principle of the parathyroid glands and the œstrus-producing hormone of the ovary have been extracted and partially purified, and methods of biological assay, which are probably roughly quantitative, worked out. Of the active principles of the testes, the cortex of the suprarenal glands and the anterior lobe of the pituitary, almost nothing is known; but our ignorance is not due to their non-essentiality, since both the suprarenal cortex and the anterior pituitary are essential to life, whilst an inkling of their functions has been obtained from human and experimental pathology.

An insight into the manufacturing problems is given by a knowledge of the properties of these hormones: insulin and the pituitary hormones may serve as a basis for the following short description. It is probable that the active principles exist in the glands in a combined form, from which they are set free by appropriate treatment; this is certainly the case with thyroxine and probably also with adrenaline. Under certain conditions the hormones will even stand boiling, but, apart from this, their main characteristic is their exceeding sensitiveness to even quite mild reagents. They are rapidly destroyed by autolysis after the death of the animal, being attacked by proteolytic enzymes, though to varying degrees.

This is also probably the reason why the majority are inactive when taken by the mouth, except in relatively enormous doses. They are extremely sensitive to alkalies, but are stable in the presence of weak acids. They appear to be either themselves simple proteins such as an albumose or polypeptide or are closely associated with them. They adhere tenaciously to precipitates formed in their aqueous solutions. Thus Dudley obtained a crystalline picrate from a concentrated aqueous solution of the pituitary hormones, which retained in full its physiological activity when re-crystallised from water: but on re-crystallisation from dilute alcohol, the activity remained behind in the mother liquor, whilst the crystals were identified as potassium creatinine picrate. Abel has recently announced the isolation of a crystalline insulin, the activity of which is two to four times greater than that of ordinary commercial insulin; the crystals bear a remarkable resemblance to cystine. Now it is known that if edestin is allowed to crystallise in a solution of insulin a great part of the activity adheres to the crystals, so that, until further evidence is forthcoming, caution should be exercised in accepting Abel's conclusion.

The principles to be followed in the production of hormones on the large scale must therefore be the inhibition of enzyme action, and the avoidance of the use of destructive reagents or the production of precipitates which remove the activity, except where the latter can be used as a method of purification with recovery of the active principles from the precipitate. The prevention of autolytic changes is best ensured by the freezing of the glands immediately after removal from the animal. The material can then be worked up at leisure and in convenient quantities, though slow changes occur in time in the frozen state, leading to lowered yields. In working up the glands, every means should be taken to prevent enzyme action: thus in the case of the pancreas, the frozen glands are minced, the acid and alcohol incorporated at a temperature of 0° C., and the whole thoroughly ground; filtration and clarification follow to remove, so far as possible, traces of adhering enzymes, and the subsequent concentration is carried out at a low pressure and temperature. In the case of the pituitary gland, dehydration with acetone at a low temperature destroys the autolytic enzymes, leaving a stable powder from which the activity can be extracted by water or dilute acid. The acidity of the solution is of great importance in the case of both insulin and the pituitary hormones. Moreover, use is made of the fact that insulin is insoluble at *p*H of about 5·0 in the later stages of the purification, so that it is essential that those working on the insulin plant should be able to determine the hydrogen ion concentration of the solutions with which they are dealing: a colorimetric method is easy to learn and gives sufficiently accurate information. In the final stages of the preparation of insulin, use is made of Dudley's method, precipitation with picric acid followed by addition of alcoholic hydrochloric acid, by which treatment the insulin hydrochloride is formed and can be precipitated with acetone as a uniform white powder.

In conclusion, reference may be made to one further point in which the co-operation of the manufacturer, the biochemist, and the physiologist may lead to important results. To obtain further insight into the chemical nature of these unknown active principles requires the provision of a moderately large quantity of relatively pure material as the starting point for further analysis. The posterior lobe of the pituitary gland of the ox weighs about 0·5 gm., of which 0·1 gm. is solid matter. Probably less than 0·1 per cent. of this represents the active principles: in other words, to obtain 100 gm. of 'pure' hormone would require the working up of glands from 1,000,000 oxen, with the probability that this material would still be a mixture of active principles and contaminating substances. Large scale working, over a course of years probably, seems the only way to accumulate sufficient material on which the biochemist can commence his research, and until the principles have been isolated in a pure condition, identified and synthesised.

The co-operation of the physiologist will be essential in tracing the course of the hormone through the necessary chemical manipulations. Moreover, until our chemical knowledge of these hormones is complete, quantitative estimation of them can only be carried out by the aid of animal tests. By the use of suitable preparations or a sufficiently large number of animals, the errors in this method of assay can be reduced within reasonable limits: thus for pituitary standardisation (on the virgin guinea-pig's uterus), the error of a single test is ± 20 per cent., and for insulin assay ± 5-10 per cent. Such differences as these would scarcely be detected in clinical medicine, so that the method of biological assay sufficiently safeguards both the physician and the patient.