Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Clinical Study of New Drugs

Sir,—Dr. G. V. Jaffé (October 6, p. 923) throws down an interesting gauntlet relating to the clinical study of new drugs.

The introduction of a new drug is a co-operative affair between many more than two professions on a business footing. Ultimately the decision of a board of directors to introduce a new remedy must rest largely on the professional advice which they receive. As practising doctors we too must largely take on trust the quality and accuracy of the professional opinions expressed by our pharmaceutical and biochemical colleagues, as we do those of surgeons, gynaecologists, and others with whom we are in more familiar professional relationship.

At consultations with his medical colleagues a general practitioner is accustomed to give the consultant all relevant information he has about the patient in question. In his dealings with his pharmaceutical colleagues, however, opportunities are rare for true consultation over new or even established drugs. The machinery which does exist is not appropriate to professional consultation. Visits by lay representatives from a drug firm, even letters to the medical staff of the firm or for publication in journals, have not provided a sufficiently free-flowing channel for the feed-back of observations from clinicians to manufacturers; nor to all those who are interested in the quality and standards of therapeutic agents, including particularly other doctors in practice.

Every prescription can be looked on as an experiment, about which notes may one day be useful. Once a new drug is being given by doctors to sick people as an appropriate remedy for their illness, whether such patients are "in a clinical trial" or not is beside the point. Any departure from the effects already known to occur after taking a drug or any unexpected sequel to the taking of a new or established drug should be reported—but to whom? Some doctors, for instance, could report the number of their antenatal patients who received thalidomide or other anti-emetic drugs in the first 12 weeks of their pregnancy, and the number of these who did not miscarry or have abnormal infants (as well as those who did). Others could report the number of similar patients who received antibiotics in the first 12 weeks of pregnancy, with details about the infant's development. At present these observations lie hidden in various medical notes like pieces of a jigsaw on a carpet. Unless and until they are gathered up and fitted together the whole picture of which each is a fragment cannot be appreciated. Eventually all such reports will no doubt be collected centrally. In the meantime the Epidemic Observation Unit of the College of General Practitioners needs such information urgently.

Nothing which is eventually done to increase the safety of new drugs can take away from each doctor—whether in general or hospital practice—his ultimate responsibility for prescribing the use of any particular drug for a patient who consults him professionally. Committees can try to improve the stringency of any tests that are carried out on each type of new drug; they can lay down (and constantly review) appropriate high standards for each class of drug; they could register and approve a special mark for each new drug to indicate that no fault could be found with the screening tests to which it had been subjected, or with the results. Such a committee could also be shown a copy of every advertisement published about each drug, whether new or long-established. At the same time a central body could be set up where reports or suspicions about unexpected effects of using any drug could subsequently be assembled for analysis and further study, and for publication where appropriate.

Control of this sort could be statutory or professional. To make any of these controls statutory would still not, indeed must not, remove from each doctor his responsible freedom to prescribe the remedy which he considers most appropriate for the patient in question. His opinion is ultimately formed and based on his professional training and experience. The General Medical Council is the statutory body already set up to delimit a doctor's professional behaviour. Is a "G.M.C." for drug manufacturers really the only way forward? After all, the existence of a statutory Food and Drug Administration did not prevent the Cutter accident with poliovaccine when it was first introduced in America.

In the post-thalidomide era nothing will ever be quite the same, either for manufacturers or for doctors or for patients. These three parties to the use of drugs should now get together round a table and decide jointly what is the best way to ensure in future that new drugs coming on to the market have been tested in the best known way and to the highest known standard. Such a joint consultative council could then take steps to get appropriate machinery set up, to carry out their proposals. It would not be a surprise if they decided to trust, first, to a tighter control by a joint professional body, composed of those with appropriate and outstanding qualifications, before asking the Government or allowing the politicians to impose "restrictive practices" by statute.

In therapeutic research (which includes the day-to-day use of drugs by any doctor) I agree with Dr. Jaffé that liaison between the different professions concerned with the manufacture, safety, and therapeutic effect of drugs has not been good in the past. In future, as well as pressing for safer remedies, we ourselves must improve the circulation of our reports about their effects, whether these be better or worse than expected. "The fault, dear Brutus, is not in our (drugs), but in ourselves, that . . ." Let us improve our own standards as well as those of the drugs we use. Thoughtful study and accurate records of his therapeutic actions should be each doctor's own prescription for himself in the post-thalidomide era; and for the professions concerned, better ways of communicating their thoughts or findings to each other.—I am, etc.,

G. I. Watson.

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Rubella in 1962

Sir,—Drs. John Fry, J. B. Dillane, and Lionel Fry have recently recorded their experiences during the outbreak of rubella in the first half of 1962 (September 29, p. 833). We feel that their remarks concerning recurrences of this disease should not pass without comment, for if we are to dispense with the belief that

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a single clinical infection will provide a long—in many instances a lifelong—active immunity, then we can no longer reassure a patient in the first trimester of pregnancy that her former attack of rubella will guarantee delivery of a baby free from congenital defects.

We believe that most physicians who have long experience of infectious diseases would agree that an attack of one of the common infectious exanthemata does provide lifelong immunity to that disease and that they will view with suspicion a history of recurrence.

Though it is probable that the rubella virus has now been identified its isolation is not yet current practice in this country. Until a tissue-culture method is available the problem of recurrent rubella must therefore be approached from a clinical viewpoint. Our own experiences may serve to throw some light on rubella and rubelliform illnesses.

During the early days of the 1962 outbreak we were impressed by the variations in the clinical features of what we at first believed to be classical rubella. Because of this we were led to make simple virus studies and analysis of case histories in the belief that not all our patients suffered from classical rubella.

As a result of our investigations we have asked and tried to answer two questions: Were all the patients sent to us as having rubella true examples of that disease, or did some have another illness associated with a rubelliform rash? Can more than one virus produce a clinical illness identical with "classical rubella"?

During March, April, and May, 1962, 81 patients, previously diagnosed as having rubella, were admitted to this infectious diseases unit. They came not because of severity of illness but because of difficulty in isolation or accommodation. They are therefore a representative selection and were not those in whom the disease was unusually severe.

Analysis shows that the records of six patients are incomplete and they have therefore been excluded. Of the remaining 75 patients 56 had classical rubella and were so diagnosed by three physicians who saw them. ("Classical rubella" was defined as a mild illness of children and young adults with a prodromal stage of less than 48 hours, a suboccipital adenitis (often tender), with or without a generalized lymphadenopathy, and a rash which first appeared on the face or neck, was locally transient, and had resolved in 48 hours or less.)

There remained 19 patients, both children and adults, with an illness which, although associated with a rubelliform rash, was in other respects not typical of "classical rubella." The prodromal stage consisted of an upper respiratory tract infection (fever, cough, rhinitis, tonsillitis), the duration of which was longer than 48 hours (average six days). The rash was first seen on the trunk or face and was more prolonged than in "classical rubella" (a duration of four days was common). General and cervical adenitis was usual, but in only four cases was it suboccipital or posterior auricular. In only one of these was there glandular tenderness. Skin petechiae were noted on the anterior chest wall and around the axillae in three cases. Six of the patients were believed to have had "rubella" before.

Virus culture from stool specimens was attempted in 51% of all patients. This included all but three of the special group of 19 patients described above. Three specimens (7%) were positive—two E.C.H.O. 14 viruses and one as yet unidentified. It is interesting that these isolations were made from that group which we have called "classical rubella," and that none came from those having the rubelliform illness described above. We do not necessarily place much significance upon these enteroviral isolations as the possible cause of their, apparently, classical rubella because healthy excretors of these viruses are found. We mention them because the association between certain enteroviral infections and rubelliform rashes is well established.

We believe that during the early part of 1962 we saw both "classical rubella" and an illness closely simulating it, consisting of an upper respiratory tract infection with rubelliform rash. We feel that the variety of aetiological agents that are now being established as the cause of a rubelliform illness may in some part account for the not infrequent "second attack of rubella."—We are, etc.,

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S. HAZRA.
J. M. MEDLOCK.

SIR,—During the recent epidemic of rubella I saw ten children who, after having had a typical attack of rubella, within 14 to 18 days from the disappearance of the rubella rash developed an illness characterized by the appearance of another rash composed of small macules. These were in colour midway between measles and rubella, and, while on the bridge of the nose and adjoining cheeks they coalesced to give a "butterfly" appearance, they remained small and discrete as they spread distally over the trunk and limbs, being particularly vivid on the palms and soles. With the exception of the coalesced area on the face, which lasted up to three days, the remainder of the rash had disappeared in 48 hours, the limbs being the last areas to clear. These children had no other symptoms or signs with the exception of cervical adenitis, which I presume was a relic of the rubella.

The rash was similar to that described in fifth disease, but I wondered if instead of being a separate entity this was an example of hypersensitivity to the virus of rubella and if such hypersensitivity might not explain the occurrence of foetal deformities following maternal rubella, such damage only occurring in the proportion of individuals responding in this hypersensitive way.—I am, etc.,

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JOSEPH BROWN.

Livedo Reticularis

SIR,—I hope that the statement in your annotation (October 6, p. 906) that "the term of livedo reticularis is appropriately applied to a rare disease of the skin seen mostly in children . . ." will not mislead readers into using this descriptive term as though it were a disease entity.

The patterning of reticular livedo is caused by capillary stasis in those areas furthest from cutaneous arteriolar supply and can occur in normal persons, particularly as a reaction to cold. In the normal state the pattern is a continuous network, but when fixed areas of a broken pattern occur the mechanism seems to be due to some interference with arteriolar supply, causing zones of increased stasis.

Polyarteritis nodosa is one cause of such an arteriolitis. Lyell and I[1] reported cases of reticular livedo and nodule formation in the skin following febrile illness which we concluded were a relatively benign form of polyarteritis nodosa in which the skin is the main target organ. The cases reported by Bradford

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